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The Journal of Allergy

VOL. 8 SEPTEMBER, 1937 No. 6

Original Articles

A METHOD OF MEASURING RATE AND DEGREE OF ABSORPTION OF ANTIGENS*

AS APPLIED TO EFFECTS OF CERTAIN DRUGS, MENSTRUA, AND MODES OF ADMINISTRATION

SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D.
CHICAGO, ILL.

DURING the course of investigations concerning the properties of an experimentally modified pollen antigen, it became necessary to develop a method showing any differences in absorption and elimination of antigens. When such a quantitative method was finally evolved, it seemed to us that it would be worth-while to employ it in the determination of absorption of extracts under conditions in which there was more or less disagreement. To allergists, interest in the degree and rapidity of absorption of antigens has always been a vital one, mainly for two reasons. One has to do with a possible modification of the mechanism of desensitization, and the other concerns more directly the practical problem of the avoidance of systemic reactions. The general problems we considered worthy of study in a preliminary way were differences in absorption in different individuals, in the same individual at different times, the effect of the menstruum in which the antigen is extracted, the route of administration, and the effects of epinephrine and ephedrine.

PREVIOUS METHODS

Previously a number of attempts have been made to measure the rate of absorption and elimination of antigens. Levine and Coca[1] sensitized passively skin sites with timothy pollen reagin, and then tested these sites with serum obtained from a nonallergic person who had been injected with timothy pollen extract intravenously. Their

*From the Department of Medicine, Northwestern University Medical School.

Read before the Thirteenth Annual Meeting of the Association for the Study of Allergy, Atlantic City, June 7, 1937.

experiments indicated a persistence of the antigen in the circulation several days after the injection, and the fact that elimination took place chiefly through the kidneys.

Tuft[2] gave intramuscular or subcutaneous injections of 50 c.c. of horse serum to three individuals, and measured the horse serum content of the blood at intervals by precipitin tests. He found that very little was absorbed at the end of the first hour, that absorption took place chiefly between the first and fifteenth hours, and that it was practically complete at the end of twenty-four hours. The horse serum remained fairly constant in the circulation for three or four days, and then it began to disappear until none was present on the seventeenth day.

Brunner and Walzer[3] demonstrated differences in gastrointestinal absorption by feeding antigens to individuals whose skins were passively sensitized with homologous reagins. Cohen and his coworkers[4-6] compared the absorption time in atopic and nonatopic subjects after blowing pollen into the nose or injecting the extract subcutaneously.

Walzer and Walzer[7] made a study of the antigen tide of food. After a feeding of a meal of peanuts the subject was injected intradermally with peanut reagin at regular and increasing intervals. This resulted in wheals which increased in their respective size for the first hour or two, diminished in the next few hours, but did not become negative until at the end of the second day. About forty-eight hours after the subject had received his last injection, he was again given the test meal. Reactions appeared first and strongest at the sites which had been injected last. The first sites failed to show reaction.

These methods of studying absorption and elimination of antigens are ingenious and helped to add considerable knowledge to this important phase of allergy. However, there are several reasons why the methods reviewed are not entirely satisfactory. The techniques of Levine and Coca and that of Walzer and Walzer are conducive to confusion because of the false immediate reactions arising from the injection of serum. The precipitin method of Tuft is, of course, not applicable to such allergens as pollen. In the remainder of the methods cited quantitative measurement of the rapidity of absorption and antigen tide are not seriously considered.

EXPERIMENTAL

Our method aimed at more quantitative estimations. After sensitizing a number of sites with serial dilutions of serum containing ragweed reagin, an injection of a standard amount of ragweed pollen extract was made at a site remote from the sensitized sites. Usually after a few minutes reactions began in the sensitized areas. The appearance time of the first reaction, the time at which the last reaction took place,

and the highest dilution of reagin at the site of which a reaction was obtained gave an indication of the rate and degree of absorption of the pollen antigen. A few days later the opposite arm was sensitized to the same serum in a similar way. Pollen was again injected, modified with the experimental question in mind, and the effects on the titer and time of reaction noted. The same experiment was repeated in several individuals.

Fig. 1.—Stages in the development of reactions in the forearm after the subject had been sensitized with dilutions of ragweed reagin and had subsequently received pollen antigen in the opposite arm. The pollen extract was injected at 9:20 A.M. The first photograph was taken at 9:37, the second at 9:48, and the third at 10:14.

A number of different serums were used, but no experiment was used for comparison unless the same serum was involved. Some of the serums were unsuitable for these experiments probably because of insufficient reagin quantity. All of them varied considerably, even in the same individual. The serum was diluted so that each successive dilution was half as strong as the preceding. Including whole serum ten dilutions were prepared, the highest dilution being 1:512.

All the dilutions of the serum were injected in 0.1 c.c. amounts intradermally on the forearm, the weakest being at the top and the strongest at the bottom. They were arranged in diagonal rows of two and marked with gentian violet for identification. The subjects used for the study were medical patients from a charity institution.* We realize that the patients were not well nor normal, but we emphasize the fact that all deductions are analyzed on comparisons of results in the same individual with the same serum.

Usually on the day following, sensitization injection of the antigen was given in the opposite arm. The amount injected was 0.5 c.c. of 1:33 dilution. We had previously found that a much smaller amount

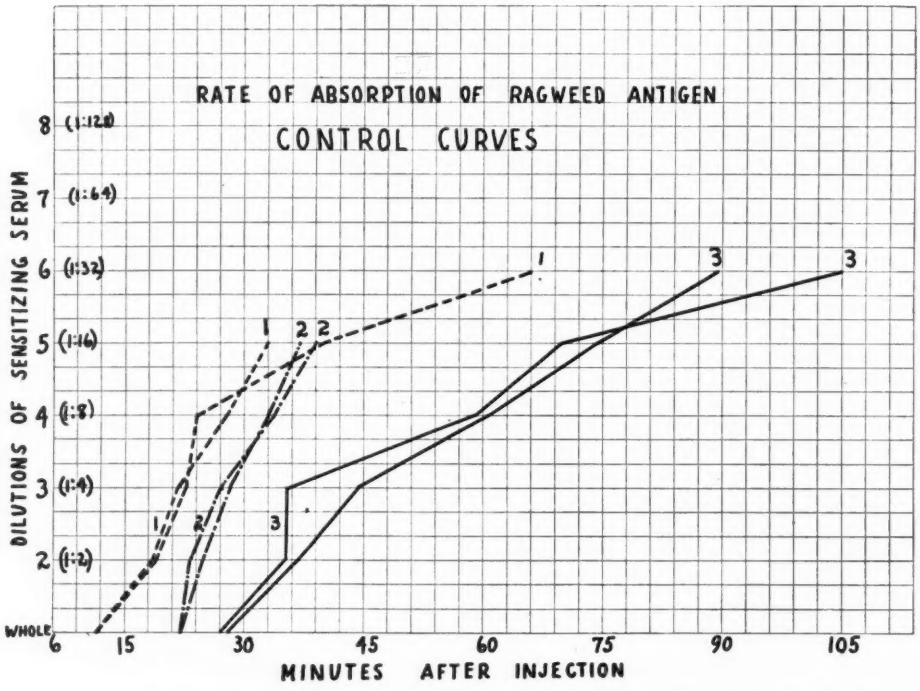

Chart 1.—Normal variations of absorption of antigens in the same individuals at different times. The beginning of the curve indicates the time of the first perceptible reaction at the site which was sensitized with whole serum. The end of the curve indicates both the height of reagin titer at which reaction took place (which indicates indirectly the height of antigen titer) and the time at which this optimum titer was reached. The graph demonstrates that under normal conditions there is very little difference in the "absorption curve" in the same individual at different times. Each number designates a different subject.

yielded very uncertain results. It may be said here that prior to passive sensitization, by history and intradermal skin test with 1:1000 ragweed extract, it had been determined that the individual was not ragweed sensitive. At times, the performance of a control test in a nonsensitized site after the serum had been injected resulted in a positive reaction, indicating an absorption of the reagin and a passive sensitization of the entire skin surface.

*On the service of Dr. S. M. Feinberg, Cook County Hospital, Chicago.

The sensitized arm was carefully watched for reactions. The factors noted were: (1) The first appearance time; (2) the time of appearance at each successive dilution; (3) the degree of the final reaction at each site; (4) the height of dilution at which reaction took place; and (5) the time of appearance of the last reaction. Invariably the site injected with the most concentrated serum reacted first, followed in turn by orderly progression of the reactions in the direction of increasing dilutions (see Fig. 1).

RESULTS

The charts illustrating the results of each of the following experiments do not contain all the data for that particular experiment, but the results are representative for the particular experiment. It was necessary, of course, to make repeated studies with the same serum in the same individuals in order to get a fair idea of the range of variation from time to time. Some of the results thus obtained are represented in Chart 1. The first appearance of reaction time is practically always uniform in the same individual providing the same sensitizing serum is used. For example, in patient No. 2 the first definite reaction appeared both times at the most concentrated site in twenty-two minutes, the farthest site reacting was site 5 (serum 1:16), reacting one time in thirty-seven minutes and another time in thirty-nine minutes. It should be noted here that we have observed circumstances under which there may be a marked variation in the same individual. For instance, a subject who usually showed the most rapid absorption and the highest titer made a very poor showing on one occasion. This was on the day following artificial fever produced by nonspecific protein. At the time of the absorption test he felt ill and chilly, and his skin was pale and cold. Needless to say, results under such or similar conditions were not used for our data presented here.

EXTRACTING FLUIDS

Because of the greater local swelling obtained with glycerinated extracts, it has been expressed on a number of occasions that such extracts are more slowly absorbed than the usual aqueous extracts. Thus Brown[8] states that "the 50 per cent glycerolated extracts take a longer time to be absorbed from the tissues than the aqueous extract because constitutionals do not occur as generally or as rapidly as with aqueous." To test this hypothesis, two sets of 3 per cent ragweed pollen extracts were made from the same dry pollen stock at the same time. One was extracted with a glycerine—Coca solution, and the other with our ordinary phenolated dextrose solution. Comparative absorption tests were made on several individuals, as recorded in Chart 2. While it does seem that in the case of the dextrose solution the first reaction appears

on the average three minutes earlier yet the curves run close together and the end points are practically identical. On the other hand, the time at which the highest concentration of antigen is found in the circulation seems to be somewhat delayed with the dextrose extracts.

ROUTE OF ADMINISTRATION

In the present discussion we shall concern ourselves only with a consideration of the subcutaneous and intracutaneous routes of injection of antigens. Is intracutaneous or subcutaneous more rapidly absorbed? Opinion seems to be quite divided on this point, most authorities be-

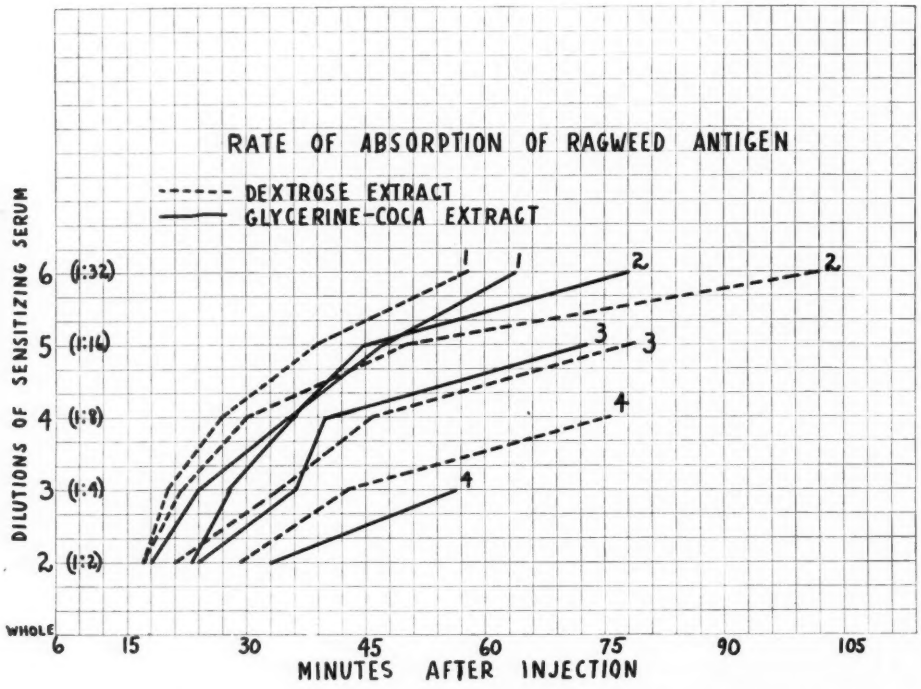

Chart 2.—Comparison between absorption of glycerinated pollen extract and dextrose pollen extract. While there is a slight delay in beginning of absorption of the glycerinated extract, the latter seems also to reach its optimum concentration earlier. As a whole it can be concluded that there is no essential difference in these absorption curves. For this series the highest concentration of sensitizing serum used was 1:2.

lieving that subcutaneous injection produces more rapid absorption. A casual inquiry of several allergists, bacteriologists, and physiologists appeared to favor the latter concept. In the recorded literature we have a number of interesting opinions. Thus Coca[9] states, "Intravenous injection of an atopen is naturally the most dangerous as the entire dose reaches the shock organ at once. Intraspinous, intramuscular, subcutaneous, and intracutaneous methods of administration rank in that order in the rapidity with which the injected substances are absorbed."

Duke[10] believes that intracutaneous injection causes faster absorption than the subcutaneous. Rackemann[11] cites an instance in which intracutaneous administration of ragweed extract in a smaller dose than the subcutaneous caused a systemic reaction. He says that "such a phenomenon might be explained by assuming that the absorption from the skin is more rapid. . . ." He adds that "On the whole, however, it is more reasonable to assume that the skin cells have a greater avidity for the allergen." In his plea for the use of the intracutaneous method of pollen therapy Phillips[12] uses as one of his arguments his belief that

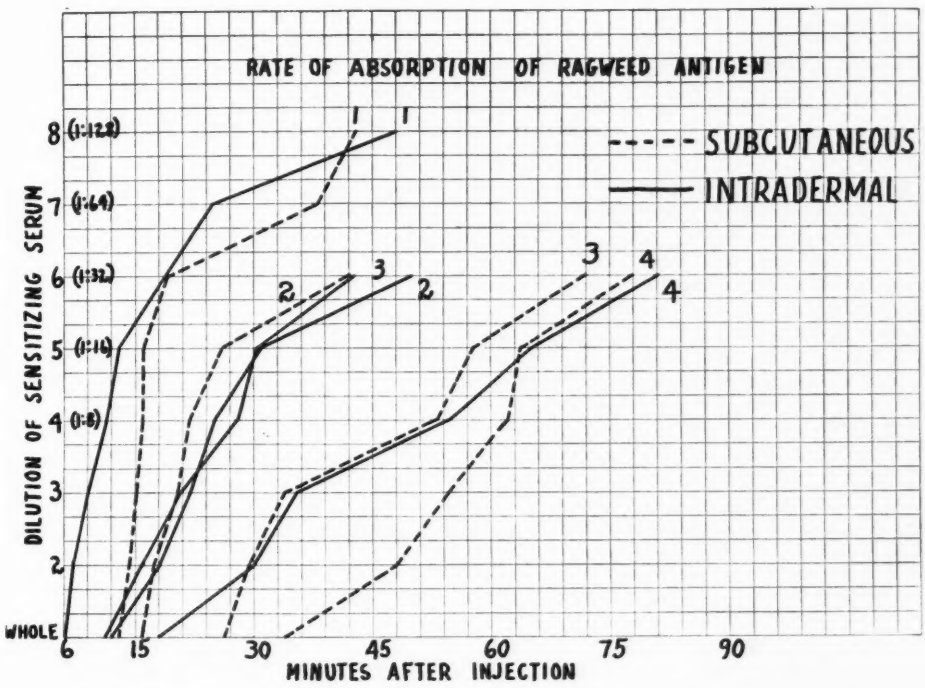

Chart 3.—In every instance the first reaction was obtained earlier by intracutaneous injection. However, in almost all instances the intracutaneous route gave a more prolonged curve.

with this method systemic reactions are avoided. He thinks that in certain people the subcutaneous route is partly intravascular.

Several individuals were used to compare absorption by the intracutaneous and subcutaneous routes. The subcutaneous injection of 0.5 c.c. of the dextrose extract was given as usual while the intracutaneous was given in two sites of 0.25 c.c. each. Some of the results are plotted in Chart 3. In every instance the first measurable reacting amount of antigen was observed earlier with the intracutaneous method. The height of antigen tide was the same in both while the time of appearance of the latter was as a rule shorter for the intracutaneous.

EPHEDRINE ORALLY

Ephedrine orally has been repeatedly recommended as a means of minimizing systemic reactions in pollen therapy. The absorption rate and the height were investigated in several individuals with and without ephedrine. The latter was administered in a dose of 3/8 grain thirty minutes prior to the injection, since it has been noted by us that the maximum effect of ephedrine therapy occurs only after about forty minutes. It will be noted from Chart 4 that in most instances such treatment has very little effect on delaying the first appearance of the reaction time. While the height of dilution at which reaction took

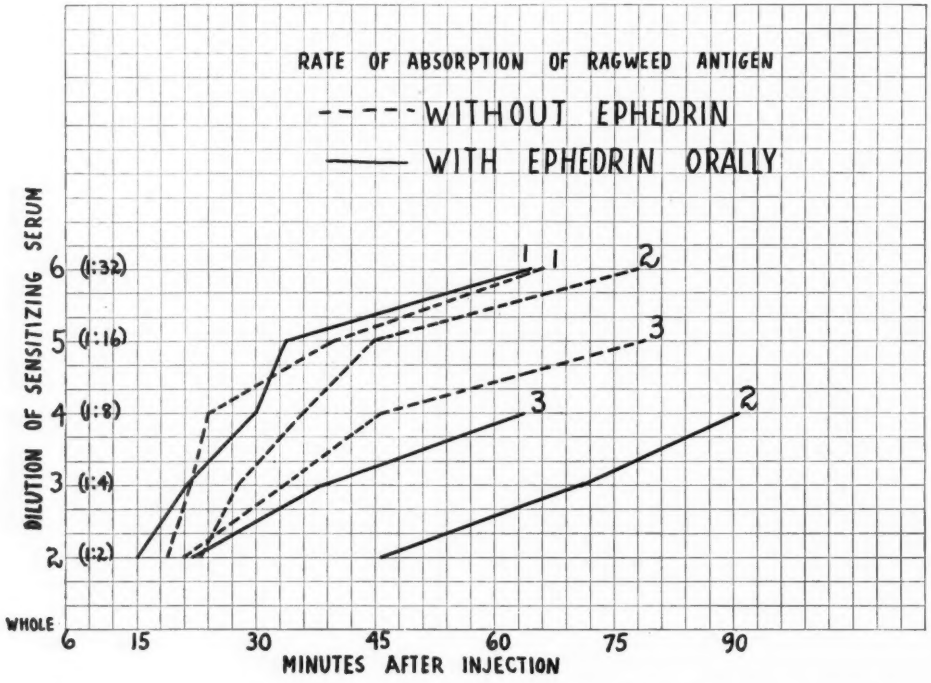

Chart 4.—Thirty minutes before the injection of the antigen 3/8 grain of ephedrine was given orally. The effect on the absorption curve is not a constant one.

place was lower in some instances with the use of ephedrine, the time of appearance of the last reaction was not particularly delayed. It may be surmised that this drug administered orally would not have a profound effect in slowing absorption and minimizing reactions.

ADRENALIN MIXED WITH EXTRACT

Duke,[10] and others before him and after him, have advised the use of adrenalin mixed with the antigen in the treatment of easily reacting individuals. The amount and technique vary with many men. Our practice has been to use 0.15 to 0.20 c.c. of adrenalin 1:1000 mixed thor-

oughly with the extract. This step has been used by us only in an occasional person who repeatedly manifests systemic reactions and whose tolerance it is impossible to increase by ordinary means. It is apparent that adrenalin administered in this manner may have two spheres of action—one, the slowing of the absorption of the deposited antigen and two, the effect of the drug on the vasomotor mechanism of the entire skin, thus inhibiting and minimizing a local skin reactivity. Tuft and Brodsky[13] have noted such an inhibiting effect on the skin reaction following the injection of adrenalin. Chart 5 shows the effect on absorption of the mixing of 0.2 c.c. of adrenalin 1:1000 with the antigen.

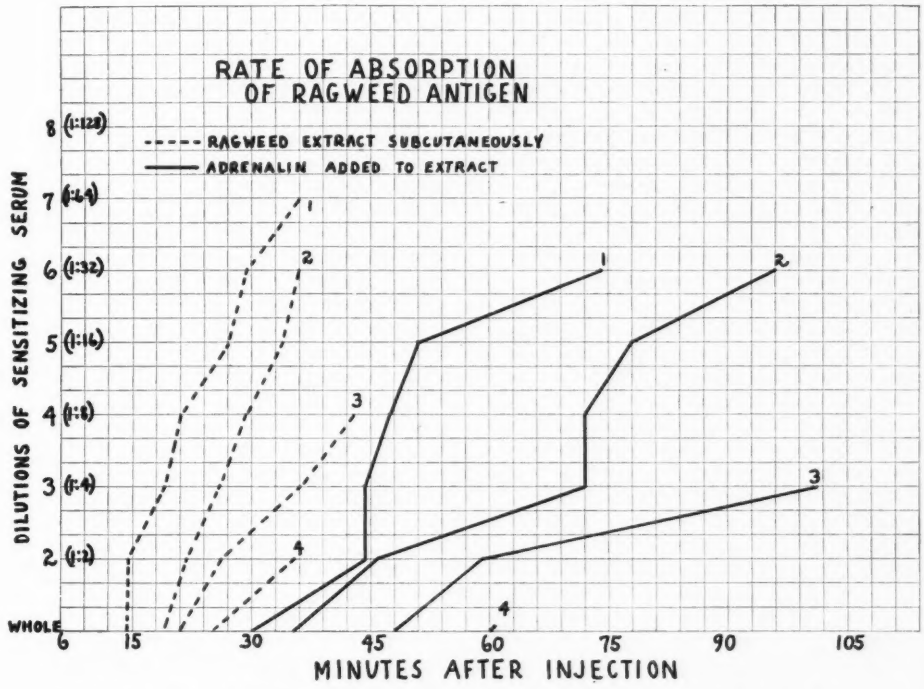

Chart 5.—The addition of 0.2 c.c. adrenalin 1:1000 to the antigen is seen to cause a marked delay in the beginning of the first reaction. There is also a tendency for the height of the titer to be diminished. There is a marked prolongation of the curve, the optimum titer being reached in a period two to three times the normal.

It will be noted that the appearance time of the first reaction is doubled on the average, and the height of the reaction occurs much later. The titer, while not as high with adrenalin, is not much different from the control curve. The curve gives the appearance that although markedly delayed in its onset the progression and the end result once it has begun is not markedly different from that without adrenalin.

ADRENALIN SEPARATELY ADMINISTERED

To determine whether the previous experiment was due to a local or a general action the following modification was used. The extract

was administered as in the ordinary manner, but in the opposite arm at the same time was injected 0.2 c.c. of adrenalin. Chart 6 shows the results obtained in several individuals. It will be seen that again there are definite delays in the first reaction time, some diminution in the height of absorption and some lengthening of the period of absorption. It would appear, therefore, that the major part of the effect of adrenalin is a general one rather than a local one.

Using the method of Cohen we determined the effect of adrenalin and ephedrine on the disappearance time of the antigen from the circulation. At the present time we are not ready to report these experiments in detail. In brief it may be said that on the average an amount of

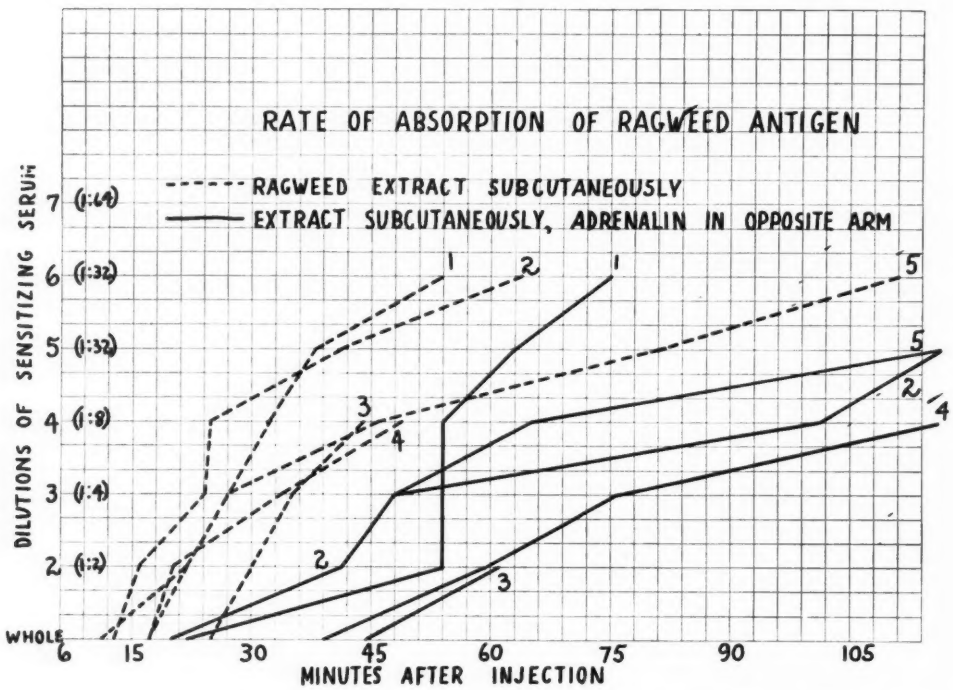

Chart 6.—In this series adrenalin 0.2 c.c. was given separately. Practically the same tendencies are displayed as in Chart 5, where the adrenalin was given mixed with the antigen.

antigen sufficient to completely desensitize a prepared site was present in the circulation as long as five to twelve hours, that from twelve to forty-eight hours this amount markedly diminished, and that after forty-eight hours none was perceptible by the method employed. Adrenalin or ephedrine had no effect on this elimination time.

DISCUSSION

We realize, of course, the limitations of the above method and of our experiments. At best the technique only exhibits the amount of antigen which when cirulating through the tissues is able to reach a

localized area in sufficient quantity to produce a reaction with the amount of reagin present locally. Furthermore, the period from the moment of the injection of the antigen to the moment of the observation of a perceptible local reaction is not really the absorption time. To be correct, it is a combination of the time required for absorption, distribution, and the mechanism of local reaction.

It should be emphasized also that all of the experiments were made on nonallergic individuals. The time factors on allergic individuals may be considerably at variance. Especially may it be the case when we are dealing with persons who are specifically sensitive to the antigen. In other words, the local tissue reaction at the site of injection may play an important rôle in modifying absorption. This needs further experimental elaboration. However, we feel because we have made it a point throughout our experiments to compare the results of each individual subject with his own control figures that these results are of some value.

SUMMARY

A method has been presented for demonstrating quantitatively the absorption rate and tide of injected antigens. Subject to the experimental conditions and limitations of this method a number of significant observations of clinical import are noted. Glycerinated extracts are not more slowly absorbed than aqueous extracts. Intracutaneous administration appears to result usually in more rapid absorption than subcutaneous. Ephedrine administered orally preceding antigen administration causes only a slight delay in absorption and has no marked effect on the prolongation of the absorption curve. Adrenalin, either administered with the antigen or separately, has a marked effect in delaying the onset of appreciable absorption and has a more moderate effect in diminishing the height of the antigen concentration in the blood.

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DISCUSSION

DR. MARION B. SULZBERGER, New York.—I am sorry that I did not have the opportunity of seeing this paper before and thus presenting a more intelligent discussion than I am now able to. However, I would like to call attention to just one point and that is the anatomy of the skin in relation to the relative speed of absorption of intracutaneous and subcutaneous injections. When discussing this paper with Dr. Feinberg and Dr. Bernstein a few moments ago, I guessed that the absorption of intracutaneous injections would be more rapid than subcutaneous ones. When one injects intracutaneously, one reaches a site which is absolutely choc-a-bloc full of small capillaries that are very permeable. The function of these capillaries immediately beneath the epidermis is to let fluids pass selectively in and out, and in that way, nourish the epidermis. The epidermis has no circulation of its own and, therefore, these subepidermal capillaries must be very permeable under certain conditions. So that this area, immediately below the epidermis, that is, this area which is reached by intracutaneous injection, is really there like a sponge, ready to absorb the material put in that site; moreover, a total large cross-section of blood vessels is ruptured and made permeable by this form of injection. When one injects more deeply, that is, into the cutis, in so-called subcutaneous injections, one reaches a site in which there are no such capillaries. Unless one deposits the antigen in the vicinity of a large blood vessel or actually in the lumen of a larger blood vessel, as Dr. Waldbott has brought out, the rate of absorption is not likely to be as rapid as from intracutaneous injection. That, of course, has been verified by the experiments of Dr. Feinberg and Dr. Bernstein and their findings correspond with the theory I have expressed and with my own experience in investigating the site and fate of substances given by intracutaneous injection.

I think that Dr. Feinberg and Dr. Bernstein correctly called attention to the fact that in these experiments they were not measuring the *absorption time*. They could not measure the rate at which the deposited allergen leaves the site of the depot, because there are two other factors involved: one is the rate at which such a substance becomes disseminated, the speed with which it reaches the reagin site; and second the latency of reaction at the reagin site.

In this connection I would like to ask Dr. Bernstein and Dr. Feinberg how they come to the conclusion that the administration of adrenalin and the administration of ephedrine delayed the *absorption time*. In my opinion, it might very well have delayed the *reaction time* at the site of the reagin depot. They simply observed a delay; which may not have been due to the fact that the deposit left the original depot site

less rapidly, but rather to the fact that the administration of the drugs in question delayed the appearance reaction through altering the state of the blood vessels or some other tissues at the site of the reagin deposit.

DR. GEORGE L. WALDBOTT, DETROIT.—This ingenious method, I believe, clarifies many a hazy question which we have been discussing for years. Some of us, for instance, still contend that intradermal injections form the basis for successful coseasonal treatment. This work definitely corroborates unpublished clinical data by myself and Dr. Freshman which demonstrate that subcutaneous and intramuscular injections are equally as effective as intradermal ones in coseasonal pollen therapy. We also learn rather conclusively that epinephrine actually does not detract from the efficacy of an injected antigen; it merely decelerates its absorption.

There are two questions which may have some bearing on the accuracy of the experimental setup: How does the absorption time vary with the size of the dose? From our experience with constitutional reactions from pollen injections, it appears rather definite that the larger the dose of the antigen the faster is its absorption time. The second point which, I believe, the authors touched upon in their paper, is whether or not the state of the patient's sensitivity may change at certain times. I wonder whether or not these two points were given sufficient consideration.

Do the authors have any data on the effect of the application of a tourniquet in influencing the absorption time?

DR. MILTON B. COHEN, Cleveland.—This paper, already rather complicated, was further complicated by Dr. Sulzberger. I have a point to make in relation to what the effect of the adrenalin is, that is, the so-called delay in the reaction in the local area.

A number of years ago when we were studying the disappearance of salt solution injected into the skin, we found that if we gave a dose of adrenalin in a distant site, salt solution was taken up from a wheal at about twice the usual rate, so that whereas the normal rate of disappearance was sixty minutes, it disappeared in thirty minutes, and conversely, if we injected histamine into the skin to produce a wheal and we gave a dose of epinephrine in a distant area, we found the wheal produced was delayed or we got about half the amount of whealing. Apparently, this is purely a vasoconstrictor effect and has nothing to do with some alteration in the reaction.

DR. C. B. BOHNER, Indianapolis.—I would like to ask the essayists if they have had any experience in the use of intramuscular injections. Those of you who have read Kahn's book, *Tissue Immunity,* will remember that he states the fixation capacity of the skin is about ten times that of skeletal muscle, and when injected superficially, much of the antigen is destroyed before it reaches the general circulation. Is there any difference therapeutically in giving an injection of ragweed intradermally or intramuscularly? Is this the reason some men can give much larger doses than others? Can the methods described in this paper be used to answer these questions?

DR. FEINBERG.—First of all, to answer the last question, we have not used intramuscular injections because of the limitation of these preliminary experiments.

With regard to adrenalin, we are all agreed. You remember that two separate experiments were made in which adrenalin was administered along with the antigen and another experiment in which adrenalin was administered separately in another site and the effect was apparently approximately the same.

Now it stands to reason, although there is no actual proof, that the effect of adrenalin, therefore, would be mostly a matter of effect on the reaction rather than absorption, because only a very small amount of adrenalin injected remotely could reach the site which was injected with antigen.

We agree, of course, with Dr. Sulzberger and Dr. Cohen, that these experiments do not measure absorption alone. We are working and have worked out a method which we are not ready to report as yet, in separating these various factors, that is, absorption, circulation time, and the time it takes for the reaction to take place at the site of the sensitization. However, for the present we feel fairly confident that this does give us some measure of the absorption rather than anything else, because we have kept the other things constant. Every experiment we have reported has been on comparisons in the same patient after the patient has been standardized a number of times. That also leads us to answer another question: How constant is a patient? The patient is fairly constant provided the conditions surrounding him are constant. We have always done our experiments at a certain time in the morning, after breakfast, between breakfast and luncheon, and the patient in the same condition, usually chronic patients in the ward.

On some occasions we have noted very marked differences. For example, in one instance a patient who had fairly constant reactions at various times and was given a fever therapy by typhoid vaccine by an interne, the next day was used for one of these tests. His reaction was very much slowed up, was about four times as slow as it had been ordinarily, but we could readily understand that because his skin was cold and clammy, there was a marked vasoconstriction of his entire cutaneous area.

We are not trying to present anything new in the way of proving anything new. We are glad that the previous clinical observations check our method. That gives us a little more assurance of using this method in further work that we intend to do.

CROSSED REACTIONS TO HOUSEHOLD DUSTS*

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POSITIVE skin tests to extracts of house dust, old kapok, old cotton linters, and old chicken feathers are common findings in almost every allergy clinic, and it is our experience that when any one of these four substances gives positive reactions, the others are likely also to show a positive reaction. Even when separate syringes are used for each extract to be tested[1] so that chemical as well as bacteriologic cleanliness can be assured, positive skin tests to dusts occur both in allergic individuals and in normal persons in from 42 to 80 per cent. The most recent figures are shown in Table I.†

TABLE I

POSITIVE SKIN TESTS TO DUSTS

The incidence of positive skin tests and of reagins to various dusts in 80 allergic patients and in 30 normal individuals.

	80 PATIENTS				30 NORMALS			
	SKIN TESTS		REAGINS (34)		SKIN TESTS		REAGINS (5)	
	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT	NO.	PER CENT
Old kapok	57	71	8	24	20	67	0	0
House dust	65	81	12	35	20	67	0	0
Old cotton linters	51	64	5	15	15	50	0	0
Old chicken feathers	54	68	6	18	13	42	0	0

In contrast to skin tests, reagins could be demonstrated in the normal subjects not at all, and in the allergic group in only a small percentage of the few cases studied. As the table indicates, the reactions to one dust seem to imply reactions to the others.

In a recent paper,[2] the immunologic relationships between different plant pollens, as demonstrated by the method of treating skin sites passively sensitized with the serum of patients with hay fever, were described. The results obtained suggested that the same method be used here to search for a possible interrelation between different dusts of household origin. Two methods of study were employed. The first was that of testing passively sensitized skin sites. From an asthmatic patient who showed large skin tests and reagins to several dusts, serum

*From the Allergy Clinic and Laboratory, Massachusetts General Hospital, Boston, Mass. Aided by the Eleanor Husted Leal Fund, Harvard Medical School, Boston, Mass.

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†In 1935, Rackemann and Simon reported that an extract of old kapok reacted in 27.3 per cent of nonallergic individuals. The present figure which is twice as high emphasizes the importance of technique.

was drawn and used to sensitize passively skin sites in non-sensitive recipients, treating the same sites with one extract or the other until desensitization was complete, and then testing the desensitized sites with some other dust extract to look for crossed reactions. The reagin content of the different serums used will be described. Fig. 1* shows the method in graphic form.

Table II shows the results observed in several different recipients when sites treated with serum 209 drawn from a patient sensitive to dusts were desensitized with one kind of dust and then tested with another. As the table indicates, there is at least one exception to the rule that

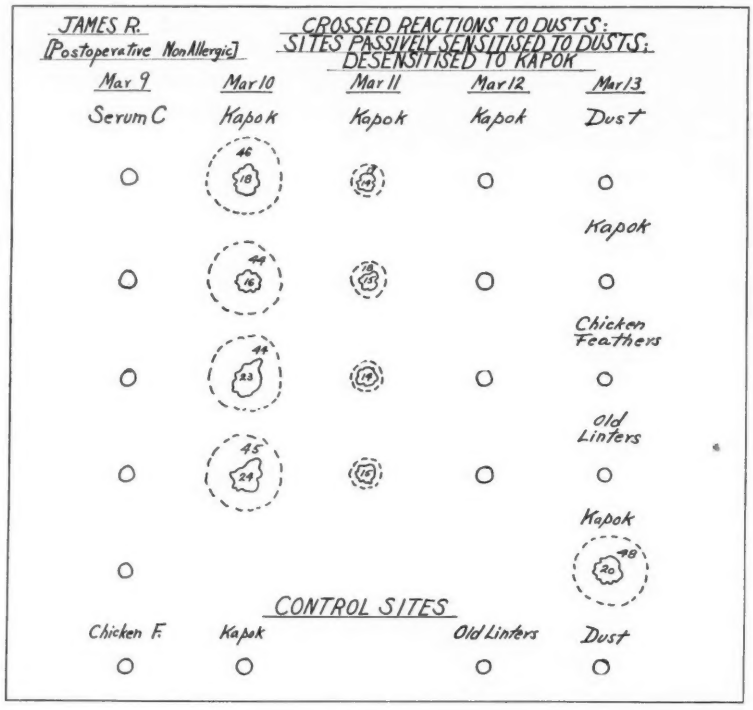

Fig. 1.

desensitization with kapok will "take care of" the other dusts. The same table also shows, that in the opposite direction, results are different; that is, desensitization to house dust does not result in or imply a desensitization to kapok.

Table III gives another series of results with different sensitive serums and using patient recipients test-negative to dusts.

With serum 209, the patient recipients showed the same result as the normal recipients summarized in Table II, but serum 215 used on three other recipients in the kapok experiment gave different results. Treatment with kapok of the sites sensitized by serum 215 did not

*Serum C is same as Serum 209.

affect the later reactions of these sites to house dust or to feathers, but the later tests to old cotton linters became negative. When these same two serums were used for the house dust experiments, the sites sensitized with serum 209 and desensitized with dust, still reacted to kapok, and one of them to old linters, whereas with serum 215, treatment with house dust seemed to "take care of" each of the three other dusts in each case. Finally, treatment with chicken feathers of sites passively sensitized with either serum 210 or serum 215, took out kapok, house dust, and old linters in all but one case.

So far, the results of this method of study fail to indicate any constant relationship between the four varieties of domestic dusts, even

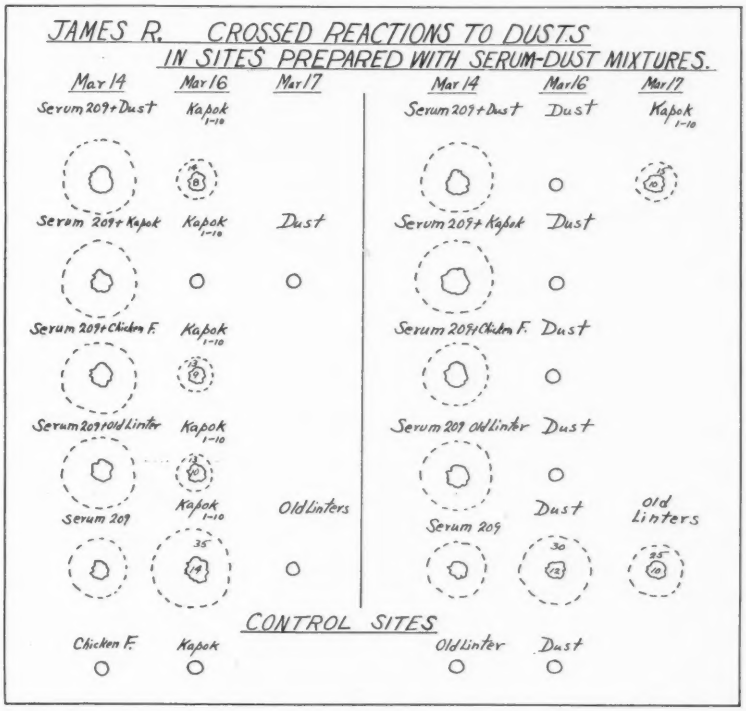

Fig. 2.

though crossed reactions do occur in many cases. These variations may depend upon the recipient, but for the most part, they are referable to the variations in the reagin content of the different serums.

The same general experiment was repeated by the in vitro method, according to which the sensitive serum is mixed in a test tube with various allergens and then the mixture is tested on the recipients' skin to see whether the reagins in the serum have been neutralized by the allergen mixed with it. Figs. 2 and 3 show the method in graphic form. With this method, a considerable series of experiments has been made with serums 209, 210, and 215 using both normal "nonallergic"

and patient "allergic" recipients. The results are presented in Table IV. In each of several recipients, three different skin sites were each injected intracutaneously with one or other of the serum-dust mixtures. Two days later, these sites were tested, each with a different dust extract. The results are shown as positive or negative. Boxes are drawn around the tests made with the same extract as used in the original serum-dust mixture.

TABLE II

CROSSED REACTIONS WITH DUSTS

Crossed Reactions to Dusts as determined by the retest of sites in normal persons passively sensitized with Serum 209 and desensitized with Kapok or with House Dust (in Vivo Method).

NORMAL RECIPIENTS						
RECIPIENT	SERUM	DESENSITIZED TO	RETEST AFTER 2 TO 3 DAYS WITH			
			KAPOK	DUST	OLD LINTERS	CHICKEN FEATHERS
1	209	Kapok		0	0	0
2	209	Kapok		0	0	0
3	209	Kapok		+	+	0
4	209	Kapok		0	0	0
5	209	Kapok		0	0	0
6	209	Dust	+		0	0
7	209	Dust	+		0	0

TABLE III

CROSSED REACTIONS WITH DUST

Patient Recipients: (in Vivo Method) Crossed Reactions to Dusts as Demonstrated by the Retest of Sites Passively Sensitized With Different Serums.

PASSIVELY SENSITIZED SITES IN PATIENT RECIPIENTS						
RECIPIENT	SERUM	DESENSITIZED TO	RETEST AFTER 2 TO 3 DAYS WITH			
			KAPOK	DUST	OLD LINTERS	CHICKEN FEATHERS
8	209	Kapok		0	0	0
9	209	Kapok		0	0	0
10	215	Kapok		+	0	+
11	215	Kapok		+	0	+
12	215	Kapok		+	0	+
13	209	Dust	+		0	0
14	209	Dust	+		+	0
15	215	Dust	0		0	0
16	215	Dust	0		0	0
17	215	Dust	0		0	0
18	215	Dust	0		0	0
19	210	Chicken F.	0	0	0	
20	210	Chicken F.	0	0	0	
21	215	Chicken F.	0	0	0	
22	215	Chicken F.	0	+	0	

As Table IV shows, the principle of specific absorption of reagins is demonstrated repeatedly. Tests of the sites with the same extract as used for the neutralization of the serum are always negative. When, however, sites are tested, not with the same but with some related allergen, the results are variable. "Neutralization" with kapok does not

prevent the later reaction to dust or to chicken feathers and regardless of whether serum 215 or serum 210 is used in the original mixture. Neutralization with house dust results, in the case of serum 215, in negative tests to kapok but not to feathers. In the case of serum 210, however, the dust allergen does not prevent the later reaction to kapok or in one case to feathers. The lower section of Table IV shows the

TABLE IV

SKIN TESTS IN NON-SENSITIVE RECIPIENTS TREATED WITH MIXTURES OF REAGIN-CONTAINING SERUM AND DUST EXTRACTS

The Table Shows the Results of Testing the Treated Sites With Various Substances. Boxes are drawn around the tests with the same substance as used for the neutralization.

SERUM	MIXTURES	RECIPIENT	TEST WITH: KAPOK	DUST	CHICKEN FEATHERS
Serum + Kapok	Serum 215	10		+	+
		11	0	+	+
		16	0	+	+
		17	0	+	
	Serum 210	22	0	+	+
		23	0	+	0
Serum + Dust	Serum 215	10		0	+
		11	0	0	+
		16	0	0	+
		17	0	0	
	Serum 210	22	+	0	+
		23	+	0	0
Serum + Linters	Serum 215	10		0	+
		11	0	+	+
		16	0	+	
		17	0	+	
	Serum 210	22	0	0	
		23	0	0	0
Serum + Feathers	Serum 215	10		+	0
		11	+	+	0
		16	+	+	0
		17	+	+	
	Serum 210	22	+	+	0
		23	+	+	0
			Controls		
Serum Alone	Serum 215	10		+	+
		11	+	+	+
		16	+	+	+
		17	+	+	+
	Serum 210	22	+	+	+
		23	+	+	+

results of similar tests on sites treated with serum alone. The positive results demonstrate the presence of reagins in the original untreated serum.

As Table IV shows, there is, by this in vitro method, little if any evidence of a crossed relationship between the various dusts. With one serum, treatment with dust removes the kapok reaction. Cotton linters also removes the kapok reaction, and it is unfortunate that the data

do not show whether kapok would remove the linters test. Otherwise the mixtures show little tendency to affect the reaction to another substance used in a later test of the treated skin site.

DISCUSSION

These results show that neither by the method of desensitization of skin sites in vivo or of "neutralization" of reagin containing serum in vitro is it possible to show any constant relationship between the various dusts used.

Tables II and III illustrating the in vivo method do show that crossed reactions occur in certain cases. Perhaps the differences depend upon the reagin content—as determined by the degree of dilution to

TABLE V*

REAGINS FOR	KAPOK	DUST	FEATHERS
In serum 209	100	10	1
In serum 210	10	40	40
In serum 215	10	40	100

*Figures indicate the number of times the serum can be diluted before reagins become undemonstrable.

TABLE VI

THE IN VIVO AND TEST TUBE METHODS OF STUDYING CROSSED RELATIONSHIP ARE COMPARED

The table also shows the differences in reagin content between serums 209, 210 and 215 (see figures on the left).

	IN VIVO			TEST TUBE		
	TEST WITH			TEST WITH		
TREAT WITH	KAPOK	DUST	FEATHERS	KAPOK	DUST	FEATHERS
Serum 209						
100 Kapok	0	0	0	0	0	
10 Dust	+	0	0	+	0	
1 Feathers				+	0	
Serum 210						
10 Kapok			0	0	+	±
40 Dust			0	+	0	±
40 Feathers	0	0	0	+	+	0
Serum 215						
10 Kapok	0	+	+	0	+	+
40 Dust	0	0	0	0	0	+
100 Feathers	0	±	0	+	+	0

which a given serum can be subjected before its power to transfer local sensitiveness is lost. Serums 209 and 215 are somewhat reversed so far as their reagin content is concerned. Serum 209 can be diluted 100 times before the kapok reagins become undemonstrable, while if it be diluted only once, its ability to transfer a sensitiveness to feathers is lost. The various reagin contents are compared in Table V.

When serum 209 is used to sensitize, its high titer of kapok reagins and its poor content of house dust and feather reagins fit in with the results. Treatment of the sites with kapok takes out the other two, while treatment with dust is ineffective so far as kapok is concerned.

When, on the other hand, serum 215 is used, treatment with kapok, to which the reagins are low, has no effect on the house dust or feather reactions to which the reagins are much higher.

By the test tube method, crossed reactions are less evident for the only "crosses" observed are that neutralization with house dust and

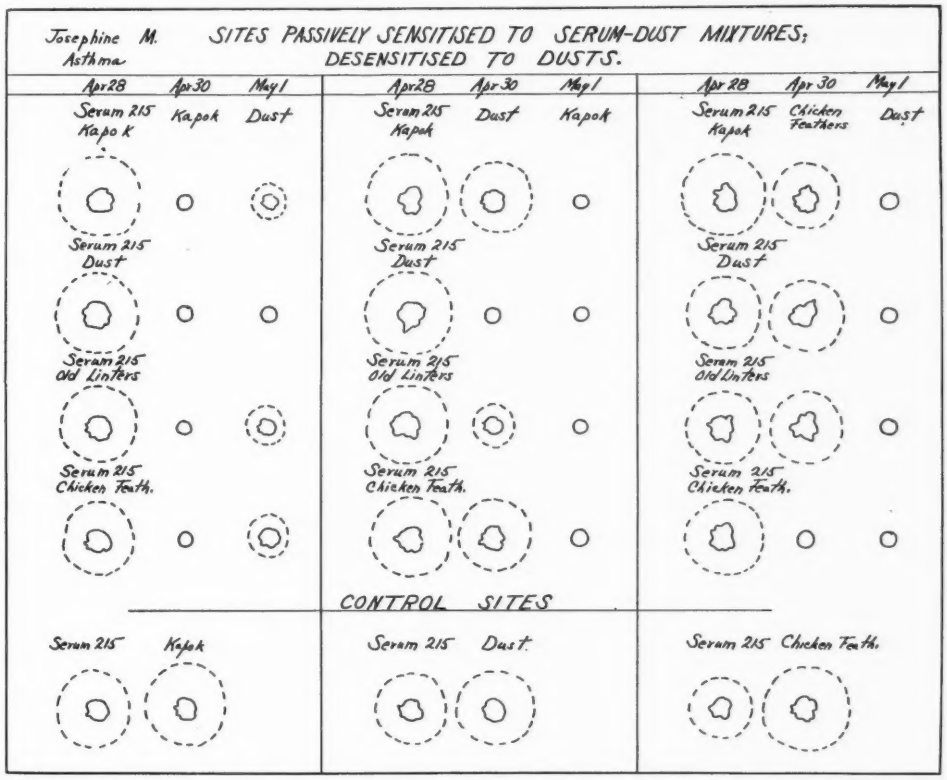

Fig. 3.

with cotton linters both seem to remove the reactions to kapok. The function of the reagin titer becomes less clear, however, when it is observed that serum 210 and serum 215 have the same reagin content so far as kapok and house dust are concerned, and yet the results with these two serums are different in several instances.

When the two methods of study are compared, the results are interesting (Table VI). Many discrepancies occur here, dependent perhaps upon the fact that the process of neutralization in the test tube is less effective and less complete than that of desensitization in the skin. Theoretically at least, the two methods of study should give the same results

especially when the same serums, the same allergen, and often the same human test subjects are used. So far as it goes, the technique seemed to be good for the reason that each particular test was repeated on several subjects and in most instances with similar results. However, we recognize that the technique is difficult and the methods so delicate that slight variations in such details as the quantities used for neutralization might give different results.

For the moment, further study seems hardly worth-while because we are satisfied that crossed relationships between these dusts do not exist except in occasional instances. In a recent study of kapok,[3] we could demonstrate that the active principle was derived from the interplay between the kapok substrate and the molds which might grow upon it; that neither the new kapok itself nor the molds themselves were sufficient to explain the clinical findings. In the present study, the house dust, the old kapok, the old cotton linters, and the feathers were obtained from different sources and could hardly be expected to harbor precisely the same flora. Moreover, Conant[4] has shown that various articles of furniture from the same environment do not necessarily harbor the same molds. The negative results of this present investigation are, therefore, not surprising. The fact that many individuals give positive skin tests to many different dust substances indicates that they have developed a sensitiveness to those substances common to their environment.

CONCLUSIONS

1. Kapok, house dust, and feathers are not identical in their biologic reaction, in spite of the fact that most patients and many normal persons react to all of them at the same time.

2. Studies of crossed relationships by the in vivo method give results which vary according to the reagin concentration of the serums used, perhaps because weak reactions are masked by stronger reactions.

3. When, however, the test tube method of direct "neutralization" is employed, results with different serums are more comparable and crossed reactions cannot be demonstrated.

4. We, therefore, conclude that house dust, kapok, and feathers do not contain any common principle which is comparable to that of the group of mammalian serum described by Simon[5] or of the group of grass pollens already referred to.

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DISCUSSION

DR. A. H. W. CAULFEILD, Toronto.—The paper really relates back to the fact that because we get a positive passive transfer reaction it does not necessarily mean that that case will be clinically sensitive. However, if the reagin occurs in high concentration then unquestionably, in my experience, clinical symptoms appear. I should like to ask Dr. Rackemann if he was able to draw any conclusion from the degree of clinical sensitization concerning the amount of reagin present.

DR. MILTON B. COHEN, Cleveland.—I am very glad that Dr. Rackemann presented this paper, because it is essentially in agreement with the point of view which we have expressed previously. There is one practical thing which we think our work and his brings out: when you make an extract of something, you must be sure to have fresh material. You cannot get some cottonseed that has been lying around, grind it up, and make cottonseed extract from it, nor can you get feathers from a bale, which may have come from China ten years ago and have been in a warehouse all that time and say you are dealing with a proper feather extract.

DR. GEORGE PINESS, Los Angeles.—This discussion brings out a point that I brought up many years ago, namely, the question of reactions to epidermal substances, particularly feathers. At that time I mentioned that it was always our policy to have our feathers obtained from kosher butchershops where they were plucked dry and in our presence, so there was not an admixture for collection of molds or other nonspecific substances at the time we were ready to extract them. Dust reactions that one gets from an individual house dust is the other thing I have fought for, for many years rather than the use of house dust from commercial chemical houses. If you are going to use house dust, use it from the source from which the patient gets it.

DR. B. GELFAND EFRON, New Orleans.—We have recently been working with ultrafiltration of the house dust and found some interesting things about house dust extract, particularly as it related to the performance of intradermal tests. We have found that nonspecific irritants, present by usual filtration, are not totally removed by ultrafiltration. The nonspecific reactions due to these irritating substances do not occur with the scratch test, but are present with intracutaneous tests even in quite high dilution. The only adequate control we have found for testing with dust extracts is not made with Coca's solution, but a dust that has been ultrafiltered and inactivated.

Another interesting thing found was that house dust allergen was quite stable and activity was only slightly reduced by autoclaving at 30 pounds' pressure, for twenty to thirty minutes. The only way we could get some practical inactivation was by treating the dust with a N/10 sodium hydroxide and then autoclaving at 30 pounds, for twenty to thirty minutes, and neutralizing with N/10 hydrochloric acid. This is quite important because many men report finding positive dust reactions in almost everyone they test.

I can get a positive reaction if I compare the reaction on everyone to the control with Coca's fluid, but if I compare the reaction obtained by the active dust, and use as the control the dust that has been inactivated, then I can read a real positive, antigenic reaction.

DR. SALVATORE J. PARLATO, Buffalo.—I should like to ask Dr. Rackemann, who has really made a very valuable contribution, whether these extracts of house dust were dialyzed or not.

DR. BRET RATNER, New York.—For many years we have taken environmental substances and soaked them in a test tube for about an hour or longer with N/10 sodium hydroxide. We have used this in the scratch test exclusively in children and have had very specific and gratifying results. The point is whether we are dealing with a true antigen reaction, because we have had true wheals represented by the tests.

DR. RACKEMANN.—Dr. Caulfeild, I cannot really answer your question because we have not made definite study of enough cases.

Part of the aspect we are all interested in is the practical one, and it does look, from our experience and from the experience of others, that it is important to extract the particular dust from the particular house that you are talking about.

Our extracts were not dialyzed. They were used fresh, but they were suitably diluted in various ways. There is one little thing on the first chart I want to emphasize, and that is the question on these eighty cases. Seventy-one reacted to old kapok, but only 14 reacted to the pod kapok. We were lucky to get an unbroken pod in the middle of the bale of kapok as it came from Java, and an extract of that, especially made, behaved quite differently, so obviously there is something that is very practical. There is a striking difference between the use of materials which are new and the use of other materials which are old and have been around the house for some time.

THE LACK OF CORRELATION BETWEEN HYPERSENSITIVITY TO EGG WHITE AND SYMPTOMS OF INJURY*

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IN A PREVIOUS paper[1] a description has been given by one of us of a pathologic syndrome attendant upon the incorporation of egg white in the diets of white and hooded rats. The fact that the animals affected have scaling skin and a tendency to scratch or rub the involved areas vigorously has led to the suggestion that these symptoms may be eczematoid manifestations of a condition of allergy to egg white, developed through sensitization by the intestinal route. The additional fact that the characteristic symptoms do not appear when the egg white has been heated at stated temperatures for sufficiently long periods[2a, b] might be interpreted as evidence in favor of this theory, since the coagulated protein could less easily find its way into the blood stream to act as a sensitizing agent.

The purpose of the following experiments was to determine whether sufficient positive correlation exists between the presence of precipitins for egg white in the blood and the presence of specific symptoms of nutritional disorder in the animal, or between the demonstration of hypersensitivity by anaphylactic shock and the appearance of these same symptoms to warrant the assumption that the presence of antibodies or the state of hypersensitivity stands in causal relationship to the recognized symptoms. It is conceded that an allergic state can exist without precipitins or anaphylaxis being demonstrable. Skin tests are sometimes used to detect such cases; and they were, therefore, undertaken in these experiments also.

EXPERIMENTS WITH RATS

Among the species of laboratory animals in which recognized symptoms of injury have been produced by feeding egg white, the rat offers one of the most striking examples of severe manifestations. In view of this fact, its immunologic reactions were investigated, even though other workers had reported difficulty in demonstrating antibodies in the serums of immunized rats and had reported small success in producing anaphylactic shock. Precipitin tests, tests for anaphylaxis, and skin tests were undertaken.

*From the State Laboratory of Hygiene and The Department of Home Economics, University of Wisconsin.
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TABLE I

Results of attempts at artificial sensitization of rats as demonstrated by precipitin tests and tests for anaphylaxis

IDENTITY AND WEIGHT OF RAT	SENSITIZING DOSES OF EGG WHITE	PRECIPITINS	INTOXICATING DOSES OF EGG WHITE	REACTIONS TO INTOXICATING DOSES
S1 Hooded 161 grams	Jan. 25—1 c.c., 5 per cent fermented, dried, intraperitoneally	Feb. 3 Negative	Feb. 9—0.6 c.c. 5 per cent fermented, dried; in heart	Nothing striking.
	Feb. 17—0.5 c.c., 1:2 fresh, intraperitoneally			
	Feb. 20 Same	Mar. 4 Negative	Mar. 5—0.5 c.c. 1:2 fresh; in heart	No abnormalities in behavior. Killed Mar. 6. Findings at autopsy, normal.
	Feb. 24 Same			
	Feb. 28 Same			
S2 Hooded 157 grams	Jan. 25—1 c.c., 5 per cent fermented, dried; intraperitoneally	Feb. 3 Negative	Feb. 9—0.6 c.c. 5 per cent fermented, dried; in heart	Death following prostration with spastic extension of hind legs and respiratory distress. Autopsy showed excessive bleeding into pericardial sac and thorax.
S5 Hooded 165 grams	Jan. 25—1 c.c., saline saturated with thymol (control on foregoing animals)	—	Feb. 9—0.6 c.c. 5 per cent fermented, dried; in heart	No abnormalities in behavior.
	Feb. 17—0.5 c.c., 1:2 fresh; intraperitoneally			
	Feb. 20 Same	Mar. 1 Negative	Mar. 1—0.5 c.c. 1:2 fresh; in heart	No abnormalities in behavior.
	Feb. 24 Same			
S3 Albino 168 grams	Jan. 25—1 c.c. 5 per cent fermented, dried; intraperitoneally	Feb. 7 Negative	Feb. 13—0.6 c.c. 5 per cent fermented, dried; in heart	Nothing striking.
	Jan. 29 Same			
	Feb. 16—0.5 c.c., 1:2 fresh; intraperitoneally			
	Feb. 20 Same	Mar. 4 Negative	Mar. 5—0.5 c.c. 1:2 fresh; in heart	No abnormalities in behavior.
	Feb. 24 Same			
	Feb. 28 Same			
S4 Albino 192 grams	Jan. 25—1 c.c., 5 per cent fermented, dried; intraperitoneally	Feb. 7 Negative	Feb. 13—0.6 c.c. 5 per cent fermented, dried; in heart	Nothing striking. Died Feb. 20. Autopsy showed thoracic cavity completely filled with fibrin and fluid.
	Jan. 29 Same			
	Feb. 17—0.5 c.c., 1:2 fresh; intraperitoneally			
	Feb. 20 Same			
S6 Albino 180 grams	Jan. 25—1 c.c., saline saturated with thymol	Feb. 7 Negative	Feb. 13—0.6 c.c. 5 per cent fermented, dried; in heart	Very inactive for one and one-half hours. Weak.
	Feb. 16—0.5 c.c., 1:2 fresh; intraperitoneally			
	Feb. 20 Same		Mar. 1—0.5 c.c. 1:2 fresh; in heart	No abnormalities in behavior.
	Feb. 24 Same			

Parker and Parker[3] were successful in demonstrating anaphylaxis in rats. For our purposes, therefore, their technique was adopted in an attempt to induce artificial sensitization. One or two doses of a 5 per cent solution of fermented, dried egg white were injected intraperitoneally. After fifteen days a test dose to demonstrate anaphylaxis was administered by the intracardiac route. This interval was chosen on the basis of the findings of Parker and Parker, which showed maximum hypersensitivity to be established between seven and eighteen days following the last injection. For the precipitin tests, the serums were used undiluted. Dilutions representing 1:10, 1:100, and 1:1000 of egg white in saline solution were made up both from fresh eggs and from fermented, dried egg white. The protocols of these trials appear in Table I.

This method did not result in the demonstration of any symptoms of anaphylactic shock. It was assumed, therefore, that the animals had not been rendered hypersensitive, and injections were continued, this time with a solution of one part fresh egg white in one part of normal saline solution, with the view of inducing antibody formation and possible sensitization. However, no precipitins were demonstrable even after the longer series of injections, and attempts to demonstrate anaphylaxis by a shock dose after this second series failed likewise. This is also shown in Table I. It was concluded, therefore, that the sensitization and immunization of rats, if they are possible, require a very delicately adjusted technique. Attempts in this direction were abandoned.

Although it seemed difficult to demonstrate anaphylaxis in the rat by the historic technique, sensitization by the gastrointestinal route was not ruled out. By feeding experiments in which egg white was administered daily in the diet of young rats from the time they were weaned it was possible to obtain animals in all stages of the pathologic sequence which regularly attends the incorporation of this protein in the diet. If there were any feeding interval or type of symptom which consistently accompanied demonstrable hypersensitivity it might reasonably be expected to be discovered by the study of such a series.

Accordingly 22 affected animals were divided into two groups, each containing cases of comparable severity, and each containing individuals affected with all degrees of severity. One group was to receive the test dose by the intracardiac route, and the other by the intraperitoneal route. Four of the animals in each group were taken off the diet containing egg white twelve days before the injection and were given an ordinary stock ration. This was done because it was thought possible for the animal to be in a temporarily desensitized state when egg white was ingested daily. The intracardiac dose consisted of 0.25 c.c. of a 1:2 solution of fresh egg white in saline; the intraperitoneal, of 0.4 c.c. of the same solution.

None of the symptoms observed following the injections corresponded with those typical for anaphylactic shock in the rat as described by Parker and Parker. Some of those which had received the intracardiac injection showed symptoms of distress involving dyspnea and weakness, but this can probably be ascribed to mechanical injury, especially since these animals at autopsy showed signs of excessive cardiac hemorrhage. It is concluded, therefore, that none of the animals investigated showed evidence of hypersensitivity by this method.

Anaphylaxis can so much more certainly be demonstrated in guinea pigs than in rats that it was considered feasible to attempt to induce passive sensitivity in them by injecting the serum of affected rats. Accordingly, intraperitoneal injections of 0.6 c.c. of serum from one rat and 0.8 c.c. of serum from another rat, both of which showed severe symptoms, were given to 2 guinea pigs. To serve as control, 2 more guinea pigs received intraperitoneal injections of 0.8 c.c. of normal rat serum. Two days later each guinea pig was injected in the heart with 0.7 c.c. of a 5 per cent solution of fermented, dried egg white. None of the animals showed any symptoms of shock. It is concluded, therefore, that the serums of the severely affected rats failed to produce passive sensitization to egg white in the guinea pigs.

In addition, nine rats in various stages of egg white injury were bled from the tail in order to test the serums for egg white precipitins. The technique has already been described. No precipitation could be detected in any of the tests.

Skin tests were done by the intradermal method on four moderately affected rats. Inoculations consisted of 0.1 c.c. of a 5 per cent solution of fermented, dried egg white in the freshly shaved abdomen. No reddening of the surrounding area was elicited during the period of observation of forty-eight hours.

Thus, no evidence of a state of hypersensitivity to egg white was obtained in rats showing symptoms of egg white injury by attempts to demonstrate anaphylactic shock, serum precipitins, passive sensitization of guinea pigs, or skin reaction.

Although the attempts along immunologic lines failed to yield significant results, it was still possible to attack the problem from a symptomatologic standpoint. For if the typical skin symptoms are due to hypersensitivity elicited through absorption of undigested egg white from the intestine, it should be possible to produce the same symptoms by the parenteral introduction of egg white. The previously reported experiment (Table I) in which almost mature rats were given several injections intraperitoneally was not adequate to throw light on this possibility, since the rats were well beyond the age when they develop symptoms of egg white injury easily, and since the amount of egg white injected could not have been sufficient to cause the symptoms.

There are no data at hand to indicate what proportion of the daily food intake of the rat may pass into the blood stream undigested. It is generally assumed that the amount is very small. We began injecting the rats intraperitoneally at alternating three and four day intervals with 0.25 c.c. of a 1:2 solution made by diluting fresh egg white with an equal volume of physiologic saline solution. The diet was a complete stock ration containing no egg white. The rats used for this purpose were started when they weighed 32 or 33 gm., just as they have been when started on an egg white ration. When they had attained a weight of 60 gm., the quantity injected was increased to 0.4 c.c. of the 1:2 solution. After forty-five days the injections were discontinued, and eleven days later the animals were killed and autopsies were performed. One of them developed a cataract on the right eye eleven days after the injections had been begun, and this animal gained weight very slowly after that; but it showed none of the symptoms of redness and bareness of the lower lip which are typical for those animals which are affected by egg white in the diet. The weights of the animals at autopsy, fifty-six days after weaning, were 214 gm.; 193 gm.; and, for the rat having the cataract, 92 gm. No other abnormalities were observed. The time interval between the beginning and end of the experiment was greater than that required for the production of symptoms of injury due to dietary egg white. The amount of protective factor in the diet was negligible.

Lest the amount of egg white injected had been too little, two more series of animals were run, which, in addition to receiving the intraperitoneal injections at three and four day intervals, received 20 per cent of dried egg white in the diet. The control group received the same diet but no injections. One of these groups, consisting of six rats, was started as usual at 32 to 33 gm.; whereas the other group comprising seven rats (three experimental; four control) weighed in the neighborhood of 60 gm. each. The object of this experiment was to determine whether symptoms of injury, if they occurred, appeared earlier in the animals which were receiving egg white intraperitoneally than they did in those which received egg white in the diet alone. As in the previous experiment, the amount injected into the small rats was 0.25 c.c. of 1:2 egg white in saline solution. This amount was increased through stages of 0.3 c.c. and 0.35 c.c. until the rats weighed 60 gm. when the amount injected was 0.4 c.c. Those rats which weighed 60 gm. at the outset received injections of 0.4 c.c. immediately.

The results, briefly, were that none of the rats developed any symptoms of injury during the thirty-two days of the experiment. After this interval they were killed and examined internally. No internal abnormality was apparent except that the spleens of all the animals seemed somewhat smaller than normal. The weights of the injected and the control groups were much alike.

We have, therefore, obtained no evidence that the injection of egg white alone or simultaneously with the feeding of subinjurious amounts results in typical symptoms.

EXPERIMENTS WITH RABBITS

Characteristic evidences of injury by egg white, which may be cured by the specific factor, have also been shown in rabbits.[4] Moreover, rabbits are known to produce demonstrable humoral antibodies very well. These animals might, therefore, be considered to be especially well suited for our undertaking.

Our efforts, in the case of this species, were confined to precipitin tests. These were run in the manner described in the section concerning rats, on the serums of a number of rabbits which were being fed egg white, both with and without the curative factor. The symptoms of injury did not appear at all or were transitory in the case of the first series of animals experimented with, because the diet had not then been perfected. In the 1935 and 1936 series the appearance of dietary symptoms occurred regularly. The various stages of injury have been described.[4] It is interesting to note that in these series, as recorded in Table II, it was not possible to demonstrate precipitins for egg white. The only positive precipitin tests occurred among the group in which the appearance of symptoms was irregular. In the 1935 series, it is possible that the animals were a little too young at the time of bleeding for optimal precipitin production; but in the 1936 series, the final bleedings were done when the animals were more than three months old, an age which is favorable for the production of humoral antibodies in the rabbit.

In brief, the results indicate that the appearance of symptoms of dermatitis in the rabbit was only occasionally concomitant with demonstrable serum precipitins for egg white. In the majority of instances no precipitins were found. It may, therefore, be concluded that the occurrence of the skin manifestations is not dependent on the production of precipitins for egg white.

EXPERIMENTS WITH MONKEYS

Abnormalities were observed in two of three monkeys whose diet contained egg white amounting to 40 per cent. Since the manifestations observed were alleviated by the administration of the specific protective factor, they are probably attributable to injury by the egg white.[4]

A blood sample was drawn on the twentieth day of feeding egg white from the monkey which showed no symptoms. From the two which showed symptoms, samples were obtained on the eighty-sixth day. On testing the serums with a 1:10 dilution of fresh egg white no precipitation was observed.

TABLE II

Development of precipitins for egg white in serums of rabbits on egg white diet

IDENTITY OF ANIMAL	DATE OF STARTING EGG WHITE DIET	DATE OF BLEEDING	SYMPTOMS AT TIME OF BLEEDING	PRECIPITIN TITER	REMARKS
ER1	Jan. 15, 1934	Mar. 28, 1934	None	1:10,000	Stage 1 symptoms Jan. 31 to Feb. 6
ER2	Feb. 12, 1934	Mar. 20, 1934	Stage 3	1:100	Spontaneous partial recovery from symptoms later
		Mar. 28, 1934	No change	1:100	
ER3	Mar. 20, 1934	Mar. 28, 1934	None	0	
		Apr. 4, 1934	None	0	
		Apr. 11, 1934	None	0	Died Apr. 14, 1934
R3	Apr. 13, 1934	May 11, 1934	None	0	Died June 30, 1934
		May 24, 1934	None	1:100	No specific symptoms
R4	Apr. 13, 1934	May 11, 1934	None	1:1000	Died May 23, 1934 No specific symptoms
ER16	May 17, 1934	June 4, 1934	None	1:1000	Never developed symptoms
ER17	May 17, 1934	June 4, 1934	None	0	Died June 12, 1934
R17	Mar. 27, 1935	June 14, 1935	Stage 1	0	
R20	Mar. 27, 1935	June 14, 1935	Stage 3	0	
R25	Apr. 24, 1935	June 14, 1935	Stage 4	0	
R26	Apr. 24, 1935	June 14, 1935	Stage 4	0	
R27	Apr. 24, 1935	June 14, 1935	Stage 1	0	
R31	Apr. 24, 1935	June 14, 1935	Stage 1-2	0	
R32	Apr. 24, 1935	June 14, 1935	Stage 1	0	
BR1	Nov. 2, 1935	Dec. 3, 1935	Stage 2	0	
		Dec. 10, 1935	Stage 2	0	
		Jan. 9, 1936	Stage 2	0	
		Feb. 24, 1936	Stage 2	0	
		Mar. 18, 1936	Stage 2	0	
BR2	Nov. 2, 1935	Dec. 3, 1935	Stage 3	0	Cure was brought about by specific factor
		Dec. 10, 1935	Stage 4	0	
		Jan. 9, 1936	Recovering	0	
		Feb. 24, 1936	Recovering	0	
		Mar. 18, 1936	Recovered	0	
BR3	Nov. 2, 1935	Dec. 3, 1935	Stage 1	0	
		Dec. 10, 1935	Stage 1	0	
BR4	Nov. 2, 1935	Dec. 3, 1935	Not definite	0	
		Dec. 10, 1935	Not definite	0	
		Jan. 9, 1936	Not definite	0	
BR5	Nov. 30, 1935	Dec. 3, 1935	None	0	
		Jan. 9, 1936	Not definite	0	
BR6	Nov. 30, 1935	Dec. 3, 1935	None	0	
		Jan. 9, 1936	Stage 3-4	0	
		Feb. 24, 1936	Recovering	0	
		Mar. 18, 1936	Almost recovered	0	
BR7	Nov. 30, 1935	Dec. 3, 1935	None	0	
		Jan. 9, 1936	Not definite	0	

Again, specific symptoms of injury had been obtained without any empirical evidence of hypersensitivity.

EXPERIMENTS WITH GUINEA PIGS

Experimental hypersensitivity demonstrable by anaphylactic shock can more easily be brought about in guinea pigs than in any other common laboratory animal. However, evidence for the specific production of symptoms of dermatitis by dietary egg white is lacking for this species. Indeed, it is doubtful whether those manifestations of malfunction which do attend the feeding of egg white to guinea pigs are at all comparable to the specific, curable injury demonstrated in the species already discussed.[4] Evidence from studies in anaphylaxis with these animals would, therefore, have value on the negative side; i. e., the demonstration of hypersensitivity in an animal which would not produce the eczematoid symptoms would show that a hypersensitive state was not always accompanied by these symptoms. It is recognized that this evidence from one species alone would be valueless; but when it is coordinated with the data already presented for other species it becomes significant.

Although it is well known that guinea pigs may be sensitized to egg white by the intraperitoneal injection of this protein, the experiment was repeated for the purposes of the work in hand, primarily in order to standardize dosage.

In the course of this preliminary work it was found that an aqueous solution of commercial, dried egg white was highly toxic on first injection. 1 and 2 c.c. amounts of a 5 per cent solution proved fatal within twelve hours of the time of injection. Post mortem findings included marked subcutaneous edema and capillary dilatation, and a considerable amount of fluid and fibrin in the abdominal cavity. The intraperitoneal administration of 0.5 c.c. of the same solution was uneventful, and 0.7 c.c. injected into the heart also produced no untoward effects. Whether the observed toxicity was due to the acidity of the solution or to the character of the protein has not been determined. However, since 1 c.c. of the 1:2 solution of fresh egg white previously described caused symptoms of distress such as heavy breathing, lying on one side with hind legs outstretched and rubbing of the nose, it may be assumed that the effect was not entirely due to acidity, in as much as fresh egg white is mildly alkaline in reaction. Moreover, Parker and Parker have also observed ill effects upon the injection of egg white and attribute them to a toxicity of the protein itself.

Sensitization was successfully brought about by giving two intraperitoneal injections of 1 c.c. amounts of the 1:2 fresh egg white solution mentioned above. Three days elapsed between the injections. Ten days after the second injection a sample of blood was taken from the

heart to test for precipitins. It was found that the serum gave a positive ring test with a 1:100 dilution of egg white. Nineteen days after the second injection 0.2 c.c. of the usual 1:2 solution was injected into the heart as a test dose. The guinea pig died within three minutes with symptoms typical of anaphylactic shock. Autopsy showed congestion of the stomach and intestines, and emphysematous lungs. There had been some bleeding from the heart puncture, but it was not excessive.

It remained to show whether the guinea pig could be sensitized to egg white by the alimentary route. A preliminary experiment consisting of the intracardiac injection of 0.4 c.c. of a 5 per cent solution of commercial, dried egg white in a guinea pig which had been fed a 40 per cent egg white diet for four weeks and showed swelling and reddening of the lips and anus resulted in the death of the animal within five minutes with symptoms characteristic of anaphylactic shock. This gave indication that such sensitization probably occurred. The experiment was repeated with 2 animals which had subsisted on the egg white diet for thirty-three days and two normal animals. One of those on the egg white diet developed marked symptoms of shock upon intracardiac injection. It did not die, but when killed fifteen minutes later, the alimentary tract still showed congestion, and the lungs were still abnormally inflated. The other egg white animal was given the test dose intraperitoneally. It developed no symptoms of shock. One-half hour later an intracardiac injection was given to determine whether the intraperitoneal dose had served to desensitize the animal. This seemed to be the case, for no symptoms of distress followed. After killing the animal with chloroform, autopsy showed nothing abnormal. Of the two normal controls, one died following the intracardiac dose, but autopsy disclosed that there had been excessive bleeding from the heart puncture. No internal signs of anaphylactic shock were evident. The other animal, which was also injected in the heart, showed only slight discomfort and no internal abnormalities.

The assumption that the reaction induced in guinea pigs by feeding egg white was truly anaphylaxis was confirmed by an experiment in passive sensitization. Three normal guinea pigs received intraperitoneal injections of blood from three which had been on an egg white diet for twelve weeks. The doses were 2 c.c., 1.5 c.c., and 1 c.c., respectively, of whole blood. Twenty-four hours later the animals which had furnished the blood and the animals which had received it, as well as three normal, untreated control guinea pigs were given intracardiac injections of the usual 1:2 solution of fresh egg white. Those on the egg white diet received 0.5 c.c. each; those which had received blood were given 0.75 c.c., 1 c.c., and 1 c.c., respectively; and the control animals were given 0.5 c.c., 1 c.c., and 1 c.c., respectively. The reactions among the egg white animals and those injected with blood were definitely more severe than among the normal controls. Two of the three on the special diet

TABLE III

The demonstration of anaphylaxis in guinea pigs fed on 40 per cent egg white diet, with and without a protective factor.

ANIMAL IDENTITY	DIET	INTOXICATING DOSE OF EGG WHITE; INTRACARDIAC	REACTION TO INTOXICATING DOSE
P17	40 per cent egg white	0.3 c.c. 1:2 fresh	Died within 3 minutes. Behavior typical of anaphylactic shock. Autopsy showed inflated lungs and intestinal spasm. Some cardiac hemorrhage.
P20	40 per cent egg white	0.3 c.c. 1:2 fresh	Behavior typical of anaphylactic shock. Did not die. Remained prostrate for one hour. Then killed. No hemorrhage.
P16	40 per cent egg white	0.3 c.c. 1:2 fresh	Behavior typical of anaphylactic shock. Did not die. Killed after one-half hour. No hemorrhage; lungs still markedly distended.
P28	40 per cent egg white and kidney protection	0.3 c.c. 1:2 fresh	Died within four minutes. Behavior typical of anaphylactic shock. Autopsy showed distended lungs and intestinal spasm. No hemorrhage.
P31	40 per cent egg white and kidney protection	0.3 c.c. 1:2 fresh	Died within six minutes. Behavior typical of anaphylactic shock. Autopsy showed distended lungs; congestion and spasm of intestinal tract. No hemorrhage.
P24	40 per cent egg white and kidney protection	0.3 c.c. 1:2 fresh	Died within four minutes. Behavior typical of anaphylactic shock. Autopsy showed distended lungs. No hemorrhage.
P35	Complete stock	0.3 c.c. 1:2 fresh	No symptoms of injury. Killed next day. Autopsy showed slight cardiac hemorrhage.
P32	Complete stock	0.3 c.c. 1:2 fresh	No symptoms of injury. Killed next day. Finding at autopsy—normal.
P39	Complete stock	0.3 c.c. 1:2 fresh	No symptoms of injury. Killed next day. Findings at autopsy—normal.
P24	Complete stock	0.5 c.c. 1:2 fresh	Fifteen minutes after injection rubbed nose, stretched and died. No other behavior symptoms. Autopsy showed congestion of the musculature of the thorax and distended lungs.
P33	Complete stock	0.4 c.c. 1:2 fresh	Symptoms of distress unlike those of anaphylactic shock. No gasping. After fifteen minutes seemed likely to recover. Then killed. Autopsy showed cardiac hemorrhage.

died in anaphylactic shock. The third one showed characteristic behavior symptoms but recovered; and upon killing and autopsy showed no abnormalities internally. The blood from this animal seemed less effective as a sensitizing agent than that from the two which died, for the reactions of the animal which received it were less severe than those of the other two in the same group. All of those in the passively sensitized group showed behavior symptoms characteristic of anaphylactic shock after having received the test dose. The one which was only mildly affected exhibited only rubbing of the nose, shaking of the head, abundant defecation, and respiratory difficulty, whereas one of the others showed all of these in more marked degree, and the third one exhibited tumbling in addition. None of these three animals died from

the effects; but all of them at autopsy, within one-half hour of their doses, showed marked congestion of the digestive tract. Among the control group, only one animal showed abnormalities in behavior as a result of the intracardiac injection. This was not like that of animals exhibiting anaphylactic shock. At autopsy, no internal signs suggestive of anaphylactic shock were found in any of the three animals.

We were convinced by the results reported above that the guinea pigs could be sensitized to egg white by the alimentary route. Thereupon we set out to determine whether or not the inclusion in the diet of these animals of the factor which had been shown in the case of rats, chicks, rabbits, and monkeys to act as protection against the occurrence of specific dietary symptoms would prevent sensitization in guinea pigs. The factor, in this instance, was introduced in the form of cooked pork kidney. As in previous experiments, an intracardiac test dose of diluted egg white was administered some weeks after the special diet had been started. The protocols appear in Table III. Briefly stated, the results show clearly that the animals which had had the protective factor included in their diet developed anaphylaxis to egg white in just as marked a degree as those to which it had not been given. This would seem to argue in favor of the lack of ability of the factor to prevent sensitization.

Intradermal tests for hypersensitivity to egg white in guinea pigs yielded negative results.

DISCUSSION AND CONCLUSIONS

The term "allergy" is usually restricted in its use to the designation of hypersensitivity in man as manifested by such symptoms as hay fever, asthma, urticaria, and numerous others. A comparable phenomenon in other animals is less well known, and consequently no technique has been described for detecting such a state in laboratory animals. The work in the present instance has, therefore, progressed along the classic lines of detecting hypersensitivity in animals, and the procedure has been drawn up on the basis of known immunologic peculiarities of the different species considered.

The data have shown no correlation between the demonstrability of precipitins or anaphylaxis and the presence of the eczematoid symptoms which are so regularly manifest in certain laboratory animals whose diet has contained egg white. Rats showed neither precipitins nor anaphylaxis; rabbits showed precipitins in only a few instances, chiefly in animals which failed to develop characteristic symptoms; monkeys showed no precipitins; guinea pigs developed anaphylaxis, but failed to exhibit symptoms which could with certainty be called specific for dietary egg white. Skin tests on rats and guinea pigs were negative.

The evidence presented in the foregoing paragraph is admittedly inadequate to prove that the specific symptoms are not the result of a

sensitization comparable to allergy; for allergy in man cannot always be proved by the methods described even when clinical evidence is strongly in favor of the existence of a specific sensitization. We believe, however, that the following consideration offers very strong evidence against the "allergic" character of the lesions in question: The characteristic lesions could not be produced in rats by the intraperitoneal administration of egg white to animals on normal diets or on diets containing subinjurious amounts of the egg white.

The protective and curative properties of food stuffs and extracts such as kidney and liver[5] may be cited as additional evidence against the hypothesis of sensitization as the cause of the characteristic manifestations. No parallel instance of protection or cure by compounds other than the protein responsible for the sensitization has been described in the field of human allergy. Moreover, our experimental evidence, in the case of the guinea pig at least, points to the inability of this specific protective factor to prevent sensitization by the alimentary route.

Thus all of the experimental evidence we have been able to gather supports the conception of the nonallergic character of the lesions in question.

SUMMARY

Attempts to induce anaphylaxis in rats by the intraperitoneal injection of egg white were unsuccessful.

Attempts to bring about anaphylactic shock by the intracardiac injection of egg white in rats in various stages of injury due to dietary egg white were unsuccessful.

Attempts to induce passive hypersensitivity in guinea pigs by the intraperitoneal injection of blood from severely affected rats were unsuccessful.

The intraperitoneal injection of egg white over a protracted period in rats on a complete stock ration or in those fed on a ration containing subinjurious amounts of egg white did not bring about the appearance of characteristic symptoms of injury.

Precipitins for egg white were demonstrable in the serums of some of the rabbits showing specific symptoms of injury, but not in all of them. The serums of monkeys showing specific symptoms of injury were devoid of precipitins for egg white.

Guinea pigs could regularly be rendered anaphylactic to egg white by the alimentary route; but specific symptoms of injury in these animals have not been conclusively demonstrated. The inclusion in the diet of guinea pigs of substances known to protect other animals from injury did not prevent the sensitization of the guinea pigs.

Intradermal tests for sensitivity to egg white in rats showing marked symptoms and in guinea pigs which had been fed for some time on diets containing egg white produced no reactions.

It is concluded that the experimental evidence does not support the hypothesis of the allergic cause of the lesions in question.

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PROPHYLACTIC TREATMENT FOR RAGWEED HAY FEVER*†

A Statistical Study

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In 1911, Noon demonstrated that the susceptibility to pollen could be lessened by the subcutaneous injection of small amounts of aqueous pollen extract. Since then, hay fever has stimulated considerable investigative work with much increase in our knowledge. However, there exists, today, considerable difference of opinion about the methods of administration and the importance of skin reactions to substances other than pollen. We feel that the present study of 612 persons who had received one or more prophylactic ragweed treatments sheds considerable light on these two problems.

The present series is limited to those who suffered clinical hay fever from ragweed and who had had at least one prophylactic treatment. A minimum of at least eight doses, the first of which was given before July 15, was arbitrarily set. Most of the series had 12 or more preseasonal doses. Unless specifically stated otherwise, the figures quoted are for the first season treated. A few had treatment elsewhere before coming to us, and a few had had phylactic or coseasonal treatment the preceding year. An effort was made to exclude those with serious allergic manifestations during the winter months. We feel, however, that many of the series did suffer from minor allergic symptoms throughout the year.

Treatment took place from 1921 to 1936, inclusive. The extracts used were made during April of each year with buffered saline solutions. For the first three years, the extracts were obtained from the New York Hospital Clinic and after that were made at Jefferson Hospital. All were considered satisfactory by skin and eye test standards.

Four hundred and eight persons were treated at the dispensary and 204 in private practice. They were not selected. All persons during these years who satisfied the above mentioned requirements were included. With very few exceptions, they spent part or all of the season in the vicinity of Philadelphia. Vacations in the north or at the seashore almost always ended long before the season.

The results of the first year's treatment of 612 persons during the sixteen-year period are as follows: Hay fever entirely or almost en-

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tirely prevented—"perfect results" 33 or 5.3 per cent (+++), greatly relieved 302 or 49.3 per cent (++), definitely relieved but considered unsatisfactory 210 or 34.3 per cent (+), and failures 67 or 10.9 per cent (0). In the following discussion, these figures will be considered "par" and will be used for comparison with fractional groups separated from the whole series. Also conclusions and percentages alone will be used in the rest of the paper and the reader is referred to the protocol for the actual figures.

A few common factors were studied and the results were, for the most part, as one would expect. Age has a deleterious effect—60 per cent satisfactory (++ and +++) under twenty compared with 52 per cent over forty. The effect is more striking in the +++ group; 12 per cent satisfactory in the younger group compared to 3 per cent in the older. Males fared a little better than females, 56 per cent to 52 per cent. The age of onset in the two sexes is strikingly different and will be discussed at length in a future paper. We can, however, say that women are most likely to develop hay fever during the period from puberty until thirty, while in males, the onset is common at all decades until fifty years of age, but reaches a decided peak from thirty to forty.

PROTOCOL

FIRST SEASON, PROPHYLACTIC TREATMENT	NO.	0	+	++	+++
Entire series 1921-36 "par"	612	67	210	302	33
Up to 21 years of age	103	9	28	54	12
21-40 years of age	329	33	115	167	14
41 years and older	174	22	61	86	5
Males	361	41	115	185	20
Females	251	26	95	117	13
Jefferson Dispensary	408	52	156	177	23
Private practice	204	15	54	125	10
Skin reaction weakly positive ("Marked" only to 0.1 mg. N. or 1000 protein units.)	54	4	17	30	3
Skin reaction strongly positive ("Marked" to 0.001 mg. N. or 40 protein units.)	354	41	121	182	10
Eye reaction weakly positive	127	13	50	61	3
Eye reaction strongly positive	67	8	27	29	3
Constitutional reactions from therapeutic injections of pollen	66	3	23	39	1
Seasonal asthma	261	26	104	118	13
No asthma	351	41	106	184	20
First year treated	173	13	65	90	5
Second (succeeding) year	173	20	58	83	12
Third year—same persons	173	15	65	80	13
Treated in 1930—total pollen Count (2100)	140	23	49	60	8
Treated in 1931—total pollen Count (3300)	146	17	65	58	6

0 —Little or no relief.
+ —Definitely relieved but considered unsatisfactory.
++ —Greatly relieved.
+++ —Hay fever completely or almost completely avoided.

PROTOCOL—Continued

FIRST SEASON, PROPHYLACTIC TREATMENT	NO.	0	+	++	+++
Low dosage, highest single dose less than 0.015 mg. total N. or 800 protein units	94	8	29	50	7
High dosage, highest single dose more than 0.025 mg. total N. or 1200 protein units	232	39	127	149	17
No pollen injections after August 20	71	1	21	40	9
Given 2 or more doses of pollen after August 20	52	1	21	29	1
Same persons, next year No pollen doses after August 20	52	2	8	34	8
Prophylactic treatment	53	1	22	26	4
Same persons, next year Perennial treatment	53	12	18	19	4
Skin reacted to animal danders as well as to ragweed pollen	48	5	14	26	3
Skin reacted to feathers as well as to ragweed pollen	131	11	45	65	10
Skin reacted to orris root as well as to ragweed pollen	145	18	50	70	7
Given injections of orris root in addition to ragweed	35	7	11	15	2
Negative skin reaction to house dust Prophylactic ragweed treatment	14	1	5	7	1
Positive reaction to house dust, no dust injections (but usual ragweed)	46	5	24	17	0
Same persons, next year, treated with dust as well as ragweed	46	6	17	21	2
Treated with dust and ragweed dust dose less than 0.5 c.c.	359	49	119	176	15
Treated with dust and ragweed dust dose at least 0.5 c.c.	239	17	86	119	17

The difference in good results between dispensary and private practice is much greater than was expected, 50 per cent to 66 per cent, although excellent results were fractionally greater at the clinic. We believe the difference can be explained largely by the synergistic effect of substances other than pollen (which will be discussed at length below). A second factor is the greater ability of private patients to avoid large pollen doses in the atmosphere. Also private patients, generally, were more faithful in their treatment and were more likely to use the nonspecific drug aids.

The more sensitive a person to ragweed on skin test, the poorer the results are likely to be. The figures are definite but not startling in all four groups. The sensitivity of the ophthalmic mucous membrane made little difference. Those, who at one time or another, suffered constitutional reactions obtained results better than "par" except that there were fewer perfect results but only half as many failures. We are often asked if greater relief is likely to be obtained in the second year's treatment. The results in 173 persons, treated three consecutive years, gives little encouragement for this hypothesis although the number of perfect results were more than doubled the second year. This, however, was offset by a noticeable increase in

the failures. The combined + and ++ figures were the same for all three years. As might be expected, the coexistence of seasonal asthma affects the prognosis adversely. This, however, is most noticeable in the + and the ++ groups. There were almost as many perfect results and slightly fewer failures in the asthmatic group.

The concentration of pollen in the atmosphere decreases the percentage of good results but not nearly so much as one would expect. In 1930 and 1931, our methods of study and treatment were the same. One hundred and forty were treated in 1930 and 146 in 1931. The pollen, however, was 50 per cent more abundant in 1931—with counts of 2,100 to 3,300, respectively. Satisfactory results were only about 5 per cent better in 1930. The complete failures, on the other hand, were about 5 per cent less in 1931 when the pollen was greater.

Great difference of opinion exists among allergists about dosage. On this, we present very definite figures. Since the minimum requirements (only eight doses before August 20) were rather liberal, many of this series, particularly in the dispensary, undoubtedly had smaller doses than we would have desired. As we have pointed out, above, those with strongly positive skin reactions did not do so well and many of these persons cannot be given large doses. For these reasons, one would expect better results in those who had received larger doses. However, the results are very definitely better in the low dosage group. The arbitrary limits of high and low dosage were—less than 0.15 mg. of N. or 800 Cooke units in the latter and more than .025 mg. of N. or 1,200 Cooke units in the former.

In the past three years, experimentally at first, the doses were stopped at the beginning of the pollen season. We now have a group of 71 who did not have any pollen injection after August 20. The results in this series are very much better than for the whole series, 69 per cent to 55 per cent satisfactory. In another group of 52, the results in two succeeding seasons were compared. In the first season, this group received at least two injections after August 20, and, in the second season, no injections were given after this date. The comparison is most striking, 58 per cent compared to 80 per cent satisfactory. However, all persons did not do better. Of the 52 persons, 22 were improved, 7 of whom advanced to the +++ classification. Twenty-four obtained the same results, while in 6, the treatment was less effectual than when the pollen was given during the season. Five of these had previously given satisfactory results. We are unable to give any clue as to who should or who should not have pollen injections during the season. We are quite convinced that the majority of persons do better without such injections.

Perennial treatment or the injection of a large dose of ragweed extract at intervals, usually of one month, throughout the year has been used by most of us as a substitute for prophylactic treatment.

In the present series, 53 persons were so treated. The results were most disappointing. Closer analysis shows that while 7 persons had a better result on perennial than on prophylactic treatment, 20 had a much poorer result. We believe this to be due to the large dose of pollen administered to them at the height of the season.

One of the greatest advances in the treatment of hay fever occurred to most workers simultaneously. This is the synergistic action of other allergens, contact with which is maintained throughout the year either without discomfort or with only trifling symptoms. We have spoken of such substances as minor "synergens" considering the ragweed as a major "synergen." So far as we know all of the minor synergens give positive skin reactions.

Many of the present series were tested with house dust, orris root, feathers, and the domestic animals with which they come in contact. When such a reaction was obtained, they were instructed to avoid contact with these allergens. In addition, many received injections of house dust and orris root. The animal and feather sensitive persons did slightly better than "par" while those sensitive to orris root gave results which were below "par." This can be ascribed to greater difficulty in avoiding orris root than either animals or feathers.

A small group (35) were treated with orris root as well as ragweed To our surprise and disappointment, this group did not do so well as those with positive orris reactions, but who had had no treatment. Upon closer analysis, however, of the 18 in whom the combined orris and pollen treatment was unsatisfactory, we found many other factors which affect the prognosis adversely. They were older. Most of them were females. They also had seasonal asthma. We feel that without the orris root injections, the result might have been even worse.

As in nonseasonal asthma and allergic rhinitis, the majority of hay fever sufferers have a positive skin reaction to house dust. We believe that it is of great importance and submit the following figures in support of this statement. We could find only 14 persons in whom the dust reaction was consistently negative. The results in this small group were much better than the series "par." Another group of 46 with positive reactions to dust were treated the first year with pollen injections alone. The second year, the pollen treatment was supplemented by dust injections. The improvement was striking, the satisfactory results increasing from 37 per cent to 50 per cent.

Another comparison was made between those receiving less than 0.5 c.c. of dust extract and those receiving more than 0.5 c.c. The results were decidedly better in those who received larger dust dosage. The improvement was most marked in the failure group, there being only half as many failures.

CONCLUSIONS

Prophylactic ragweed treatment is more likely to give good results: (1) In males; (2) in younger persons, particularly below twenty years of age; (3) in private practice; (4) in those with weaker skin reactions; (5) in those who have had constitutional reactions; (6) in those who have never had asthma; (7) when the maximum dose is low—less than 800 Cooke units or 0.015 mg. of total nitrogen; (8) when ragweed injections are omitted during the season, although a few persons do better with these coseasonal doses; (9) and when other allergens, acting in a synergistic fashion, are discovered and appropriately treated.

Prophylactic ragweed treatment is but little affected by (1) the strength of the eye reaction; (2) the atmospheric pollen concentration; (3) successive years of treatment.

Perennial treatment was much less satisfactory, on the whole, than prophylactic although a few persons do better on this form of therapy.

DEFICIENCY OF ATMOSPHERIC HUMIDITY AS A CONTRIBUTING FACTOR IN PROLONGED ASTHMA

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THE ordinary attack of bronchial asthma is readily recognized. It is of comparatively short duration because it is promptly relieved by the use of simple remedies. Relief may also be produced by the withdrawal of specific allergens. There are some patients who, despite these ordinary measures, experience moderate to severe asthma continuously from several days to one or two weeks and even longer. During all this time, they are never symptom free.

For several years I have noted certain pertinent clinical data. These prolonged attacks occurred chiefly during the colder months, in children as well as adults although they were more frequent in the latter. The nose, throat, and even the larynx always revealed a marked dryness of the mucosa with collections of inspissated mucus or mucopus. Furthermore, this condition was noted in allergic cases with either infected or noninfected nasal sinuses. Their skin was dry and rough. A search into this problem was instituted early last fall. Studies led to a consideration of the relative humidity of the air. Incidentally, the question of the efficacy of atropine and allied drugs as relief measures presented itself as an additional but more or less correlated problem. For the purposes of this paper, I am excluding cases of status asthmaticus, such as occur following an injection of antitoxins, the ingestion of foods by an extremely sensitive child, etc.

Much has been written about the influence of climate, temperature, and other atmospheric changes upon the asthmatic patient. Those residing in sections of the country where considerable heating of the home is necessary for four to six months often are advised to go south because the warm, equable temperature may help them. The same patients during the summer months may be told to go north or to cooler parts of the continent. However, for economic reasons, this method of relief is not always possible. I shall try to show that it is really the control of humidity which plays an important rôle in relieving these patients. The introduction of air conditioning has been a long step in the right direction for the ultimate solution of this problem. By removing allergens from the air, such as pollens and dust particles, hay fever and asthma sufferers have been helped. It was soon realized that the control of humidity as well as of the temperature added to the comfort of these patients. Experiments which have been reported so far were conducted during the summer months when the increased humidity caused con-

siderable annoyance. Therefore, efforts were made to reduce the relative humidity as well as to cool the temperature. Vaughan and Cooley[1] reported that a relative humidity of 55 per cent with a temperature varying from 68 to 71° F. proved satisfactory. They used a well-known commercial air conditioning apparatus. Criep and Green[2] employing an electrostatic cleaner reported success in relieving pollen and house dust sensitive persons. However, they made no provision to control the humidity nor the temperature. Rappaport, Nelson and Welker[3] emphasized the full significance and importance of adjusting the relative humidity as an aid in pollen asthma.

Several constant factors may be noted in the above reports. First, the experiments were carried out during the summer months; second, the

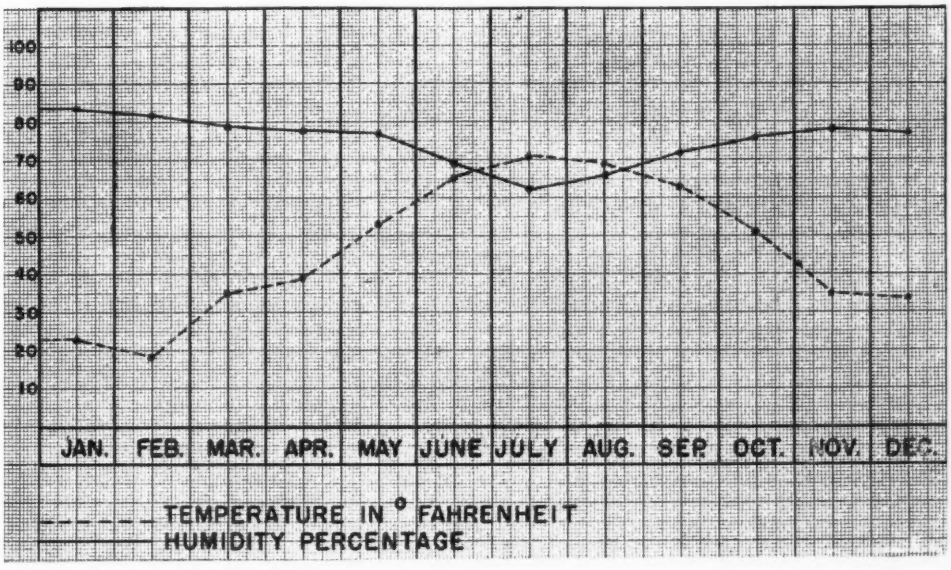

Chart 1.—Relative humidity and temperature readings for Buffalo, N. Y., as compiled from the United States Weather Bureau Reports for 1936.

temperature as well as the relative humidity was lowered. One is made comfortable where the air is so treated because the minute allergens are removed and a steady current of air of mild velocity aids in cooling and dehumidifying the atmosphere. In this paper we are concerned with the effects of the lack of sufficient humidity and of raising the temperature during the colder months of the year. These ill effects multiply when we consider the many homes and offices where little or no ventilation is permitted throughout the entire winter.

At this point a few definitions are in order. Humidity is the term which is used to describe the water vapor or moisture in the atmosphere. Absolute humidity is the actual amount of water vapor and is expressed as the number of grains of water per cubic foot of air, the atmospheric

pressure being about 15 pounds per square inch. Meteorologists have determined that under normal pressure air at 0° F. will hold half a grain of water vapor per cubic foot, at 32° about two grains, at 70° eight grains, and at 100° F. about 20 grains of water. One speaks of relative humidity as the amount of water vapor in a unit volume of air space compared to the total amount which could be contained in the same space under the same conditions of atmospheric pressure and temperature. It is expressed in percentage. For example, if air in a home or office with a temperature of 70° F. has a relative humidity of 25 per cent, it means that each cubic foot holds only two grains of water or one quarter of its known maximum capacity. This is common during the winter. Out doors on the same day the temperature may be 32° F., and the relative humidity 75 per cent. It means that each cubic foot of air

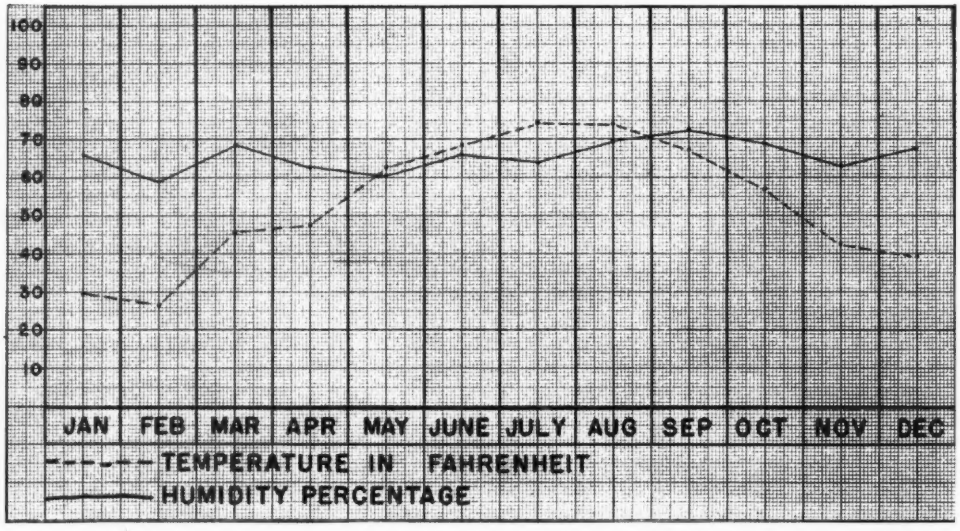

Chart 2.—Average relative humidity and temperature readings for New York City as compiled from the United States weather bureau monthly reports for 1936.

would contain approximately 1½ grains of water. In the way of contrast, I have found that during the summer months the relative humidity averages close to 65 per cent. But, since the temperature is higher, the total amount of air moisture is actually greater, hence the discomfort of the sultry summer days. (Chart 1.) As a matter of fact, the air of the summer—indoors and outdoors, contains 3 to 4 times as much moisture as is found during the colder months of the year.

In Chart 2, I have prepared a graph of the average relative humidity and temperature readings for New York City during 1936, so as to compare them with those of Buffalo. In general, the temperature is higher and the relative humidity lower in New York, hence it is damper. I think that this observation coincides with the common belief of most New Yorkers.

Outdoors this moisture is supplied by evaporation from lakes, rivers, melting snow, and from every living plant and animal. In homes and other buildings, water moisture is obtained from cooking foods, hot water, baths, furniture, house woodwork, plants, etc., and from the natural moisture of the human skin as well as from the respiratory tract.

There are several types of instruments which are commonly used to record the relative humidity, such as the "Humidiguide" for direct reading, the wet and dry bulb indicator, and the sling psychrometer. The reading of the latter two is calculated from certain known tables. I have found the wet and dry bulb humidity indicator both accurate and economical. Humidity readings were made in offices, homes, theatres, hotel rooms, hospital rooms, etc., from November 1, 1936, to March 1, 1937. As tabulated in Table I, I have found the relative humidity as low as 15 per cent with temperature ranging between 65° and 80°. The usual finding was 20 to 30 per cent. Normally it should be

TABLE I

TEMPERATURE AND RELATIVE HUMIDITY AS FOUND IN VARIOUS INDOOR PLACES NOVEMBER 1, 1936 TO MARCH 1, 1937*

	TEMPERATURE	RELATIVE HUMIDITY
1. Apartment house room	75	23
2. 11 patients' homes	71	25
3. Office building	74	24
4. Theatre	70	37
5. Hospital room	71	30
6. Interne's room	74	36
7. Author's office	73	39
8. Hotel room	75	24
9. Department store	72	40
Average	72.7	30.3

*These figures are the averages of two or more readings made on different dates of the month.

40 to 55 per cent. In other words, the air of those places in which we live during the winter months was found to contain nearly one-half the amount of moisture which is necessary for comfortable healthy living. A drop of 15 to 20 per cent of humidity is readily noticed. Take a piece of furniture for an example. The aridity of the air causes moisture to be drawn from the glued portions of the furniture, causing a loosening of its parts and eventually a breakdown. A cigar or cigaret left exposed will dry very rapidly. For this same reason plants need more watering. The effect on the human being is quite pronounced. The skin becomes dry and rough. The mucous membranes of the nose and throat feel dry and stuffy. Considerable inspissation of mucous and mucopus occurs, particularly in the nasopharynx. Crust formations in the nose lead to recurring nosebleeds. The deleterious effects of this condition upon a patient with an ordinary head cold are quite apparent. It is my further belief that this dry irritating air may account for some

of the coughs which accompany the common cold and may delay recovery in some instances. A point to be remembered is the real aid which is derived from the use of steam inhalations, steam kettles, etc., in the treatment of upper respiratory infections.

With the asthmatic patient, this lack of sufficient air moisture plays an important rôle in prolonging the paroxysm. Essentially, the mechanism of the asthmatic attack is a protective reaction by the respiratory tract to any allergen. It may result in the production of edema of the mucous membrane, overactivity of its mucous glands, or a spasm of the muscles of the bronchioles, alone or together. The rate of breathing is increased, so that, in an atmosphere of low humidity, there is a considerably greater loss of moisture from the bronchial tubes. This contributes to an early change in the nature of the mucous secretions. The latter become viscid and tenacious. Bronchoscopic examination during this stage of an attack will reveal this thickened, gelatinous secretion in the trachea and bronchi. Hansel[4] states in his comprehensive book, "The dryness of the mucosa and the marked tenacity of this type of accumulated secretion explains the comparative lack of sputum and the difficulties encountered by the patient in coughing up this material. Attempts to dislodge this secretion from the bronchi tend to further excite the asthma." It is then this difficulty in raising phlegm, thus formed, which constitutes an important factor in protracted asthma. I have found that of a total of 51 asthmatics between November 1, 1936, and March 1, 1937, seven patients presented themselves with severe asthma, the lack of humidity causing the prolongation of the symptoms. There were a few other patients in whom this factor operated in a milder form and were, therefore, not included in this report.

Bearing this picture in mind, it would seem that the use of atropine, belladonna, and allied drugs would be contraindicated in the treatment of asthma. The depressing action of these drugs upon the mucous glands of the respiratory tract actually aggravates the asthmatic symptoms. Peshkin[5] believes that atropine does more harm than good. The frequent inhaling of asthma powder smoke which contains belladonna or stramonium or the repeated hypodermic injections of atropine gr. $\frac{1}{150}$, which is usually combined with morphine, causes very distressing and protracted cases of asthma. In my series of 51 patients already alluded to, there were four cases where combined with the insufficient air moisture, very severe prolonged asthma developed. These patients, all adults, presented typical symptoms, such as dilated pupils, parched tongue, dry, glaring red mucosa of nose, pharynx, and trachea with strings of tenacious secretion, unproductive cough, distressing breathing with some cyanosis, rapid pulse, dry skin, and in one case, an elevation of temperature which is sometimes caused by atropism. Whenever these symptoms are recognized, the immediate withdrawal of these drugs is indicated.

The treatment of prolonged asthma due to low humidity, whether or not intensified by the administration of atropine, calls for the prompt and adequate addition of moisture in the air, and the administration of sufficient liquids to the patient. The temperature of the room should be kept around 70° F. The relative humidity is maintained between 40 and 55 per cent. This has been accomplished by one of several simple and inexpensive ways. Where a hot air heating system is used, the jacket of water around the heated air chamber of the furnace should be large enough and be kept filled all the time. Moisture obtained in this way usually needs to be augmented by the use of pans of water near the hot air registers. This proved successful in four cases. In the three other instances where steam or hot water systems were in operation, the desired humidity was obtained by the use of water pans on the radiators, evaporation being facilitated by small electric fans. There are several types of commercial portable humidifiers which could be used satisfactorily. With the relative humidity maintained within the normal range, the temperature need not be more than 70° to 71° F. to assure warmth and comfort for the patient.

Five patients who were treated at home under improved air conditions, responded more readily and more rapidly to symptomatic treatment. These patients had had asthma more or less continuously from three days to two weeks. One seemed adrenalin fast. Another had tried the inhalation of adrenalin vapor without success. Injections of adrenalin gave little relief for only one-half to two hours at a time, even when it was combined with small doses of morphine sulphate. In two instances, the latter had to be discontinued because some cyanosis was noted. Rectal instillations of equal parts of ether and olive oil had been administered to two cases but eventually were discontinued because colitis had set in. The remaining two cases were so dehydrated and so desperately ill that they were hospitalized. Water was administered by hypodermoclysis. Two to three liters of 5 per cent dextrose in normal saline were given within the first twenty-four hours. Tap water enemas were also given to clean the lower bowel and to supply possibly additional water. These two cases also received intravenous injections of 20 c.c. of sodium iodide 10 per cent solution. Within twenty-four hours, the mucous membranes of the upper respiratory tract became moist, the flow of mucus was restored, phlegm was raised, and the expectoration and breathing were easier. At this point, the hypodermic injections of adrenalin in doses of 5 to 8 minims began to take hold and the asthma disappeared.

SUMMARY

1. A lack of sufficient air moisture or relative humidity in our well-heated homes and other indoor places during the colder months, is an important factor in the causation of prolonged asthmatic attacks.

2. The use of belladonna, stramonium, and allied drugs often is contraindicated. The latter are to be used only with great caution. Their paralyzing action on the mucous glands of the respiratory tract aggravates and delays recovery from an asthmatic attack.

3. Treatment calls for the immediate withdrawal of any of the above named drugs. Methods of supplying an adequate amount of air moisture are described. It was found that with a normal relative humidity patients responded more readily to the usual therapeutic measures which are used for the relief of asthma. Subsidence of prolonged asthma is more prompt and effective.

4. A wider distribution of accurate air conditioners in homes and places of industry and business will provide a very necessary and important means of maintaining a correct temperature and relative humidity, thus helping to reduce the number and duration of prolonged asthmatic attacks.

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ON THE POSSIBILITY OF AN ALLERGIC FACTOR IN ESSENTIAL HYPERTENSION

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ALTHOUGH there is no constant or characteristic alteration of the blood pressure in clinical allergy, the pressure in the intervals between the acute allergic episodes is said usually to be normal or subnormal. Vaughan[1] observed in a series of allergic individuals with asthma, eczema, vasomotor rhinitis, and urticaria, whose symptoms were relieved following allergic therapy, that 20.5 per cent had a systolic pressure below 110 mm. Hg; 59 per cent were between 110 and 145; and 20.5 per cent had pressures above 145. Among those not benefited 27 per cent were below 110, 8 per cent above 145, and the remainder or 65 per cent within the normal range (110 to 145). Duke[2] found in his series of pollinosis cases that the systolic blood pressure was normal in 40 per cent, below normal in 43 per cent, and above 150 in 17 per cent. In 2 cases the systolic pressure was above 200 mm. Feinberg[3] states, "The general tendency for blood pressure in allergic conditions is to be low."

Most of the discussions of blood pressure responses in allergy have dealt with findings in bronchial asthma. Alexander[4] states, "at the height of an asthmatic seizure there is usually a fall in blood pressure. Between paroxysms the blood pressure tends to be below normal. It is the exception to find increased pressures." In a series of 50 cases Alexander found only three with high systolic values ranging from 150 to 170 mm. The average was 118 systolic, 74 diastolic. The average age was thirty-nine years. Sihle[4] also describes a fall in blood pressure during the asthmatic attack. Rackemann[5] states, "a low blood pressure is common in asthma." Walzer[6] writes, "it is generally admitted by most authorities that the blood pressure in asthma is usually normal or subnormal in the free interval between the paroxysms. Hypertension, however, is not an uncommon accompaniment of bronchial asthma."

Others describe an increase in blood pressure during the asthmatic seizure. Cooke[7] states, "between the attacks the blood pressure, both systolic and diastolic, is frequently low. When the readings are made during a paroxysm the systolic pressure is usually elevated, and this is due to the extraordinary effort at respiration." Feinberg writes, "during the asthmatic paroxysm as a rule the pressure rises and varies markedly with inspiration and expiration." Kahn[8] has described four patients with hypertension associated with severe intractable asthma in

whom the administration of adrenalin was followed not only by relief from the asthma but also by a fall in blood pressure. In one case the systolic pressure fell from 200 to 140 mm. following the administration of 25 minims of epinephrine in a single dose. In another with initial systolic pressure of 260 mm., one c.c. of adrenalin was given every fifteen minutes for four doses and then every thirty minutes for an additional two doses. At the end of this time the asthma was considerably relieved, and the systolic pressure had fallen to 175 mm. Later it fell to 148 mm. In his third and fourth cases, systolic pressures of 170 and 190 mm. fell gradually after several days of adrenalin therapy to 138 and 150 mm., respectively. He did not describe diastolic response. Cooke found that when hypertension accompanied asthma, the diastolic readings were not correspondingly elevated. He also observed that epinephrine promptly reduces the blood pressure.

These observations would indicate that hypertension is sometimes an accompaniment of the asthmatic paroxysm. The evidence does not enable one to determine whether the pressor response is a part of the allergic picture itself or whether it is, as suggested by Cooke, merely the result of respiratory effort.

Very little indeed has been written concerning the incidence of allergy in persons with essential hypertension. Kerppola[6] found 5 per cent of 200 cases of essential hypertension to be asthmatics. Twelve of his series experienced an increase in pressure of from 25 to 100 mm. Hg during the asthmatic attack. At these times adrenalin administration was followed by a rapid return to the lower pressures.

Waldbott[9] studied a young woman, aged thirty years, of a family many of whom suffered from hypertension and allergy. This woman four years previously had had a systolic pressure of 185 mm. At the time of Waldbott's first examination the blood pressure was 212 systolic, 115 diastolic. She was found allergic to milk, peas, beans, salmon, rice, and chocolate. Following the elimination of these articles from her diet, the pressure gradually fell to 145/92, and the allergic symptoms subsided. During the succeeding two years in which she followed her allergic restrictions, the systolic pressure ranged from 145 to 152 mm., the diastolic remaining around 90. At the end of this time the pressure again rose to 195/118. It was found that she had developed new sensitizations, to rabbit hair, horse dander, camel hair, glue, and coffee. In her occupation she was exposed to most of these substances. She was unable to change her occupation but remained strictly on her diet, avoiding the other allergens so far as possible. During the succeeding six months the systolic pressure usually ranged below 150 mm. By the end of this time the diastolic had gradually risen to where it usually read around 107 mm.

In another case not studied over as long a period, dietary allergic restrictions were followed by a drop in pressure from 192/108 to 138/92 mm. This patient was a girl but fourteen years of age.

Lee P. Gay, in an exhibit on the leukopenic index before The Southern Medical Association (1935), presented charts showing the fall in blood pressure in a case of hypertension following avoidance of demonstrated allergenic foods, with temporary return of increased pressure with nonavoidance.

These few reports indicate that hypertension may occur in allergic individuals and vice versa; that in acute allergic episodes at least, adrenalin administration may be followed by a diminution of the increased pressure; and that in allergic cases with essential hypertension, prolonged avoidance of the allergenic excitants, especially foods, may be accompanied by a prolonged remission in the hypertension.

PRESENT OBSERVATIONS

During the summer of 1936, one of us made an intensive study of an allergic patient with hypertension.

CASE REPORT

A man, aged forty-five years, had first been examined in 1930, at which time his chief symptom was an allergic dermatitis. At that time his blood pressure was normal. Within the three ensuing years he developed a definite hypertensive tendency which by 1936 was definitely established, his systolic pressure at that time ranging from 150 to 180 mm. Hg; diastolic 100 to 110 mm.

Skin tests with foods had been made in 1930, 1933, and 1935 and were repeated in 1936, at which time the hypertension was being studied as a possible allergic manifestation. In 1935, leukopenic indices had been made to wheat and coffee, both of which were positive.

During the 1936 study, skin tests were made with all of the foods customarily eaten, a number of leukopenic indices were recorded for those foods which the patient ingested more frequently, and, for a period of eight days, blood pressure determinations were made at intervals varying from thirty minutes to three hours, throughout each day, from 8 A.M. until retiring time.

Each morning at breakfast time a leukopenic index determination was made following the ingestion of a single food or a food mélange. During this determination blood pressure recordings were made every thirty minutes. Lunch and dinner each time consisted of various foods, all of which were listed. The blood pressure response before and following these meals was noted.

Chart I shows the blood pressure curve throughout the period of observations. Foods listed on the chart are those which were ingested prior to pressor responses. On the first two days, Tuesday and Wednesday, pressor responses followed the ingestion of meals or food mixtures. Thus on Tuesday mustard appeared to be responsible because it had been previously strongly positive by skin test, but pork, ingested on Wednesday, was also positive. It, therefore, became obvious that for most accurate information, the response to individual substances rather than food mélanges should be followed. Therefore, after Wednesday only

individual ingestants are indicated. These are not all of the foods that were eaten but are those which were followed by an increase in blood pressure. The times at which they were eaten are indicated on the systolic curve by the horizontal breaks.

The variation in diastolic pressure is not indicated on the chart, since it was not pronounced. The diastolic range was from 102 to 110 mm., and followed the systolic quite consistently in its ups and downs.

The pressor response to alcoholic beverages merits especial attention. Alcohol has in the past been incriminated as one of the causes of chronic or essential hypertension. In this case, however, it was observed that one form of alcohol, Scotch whiskey, not only caused no pressor response

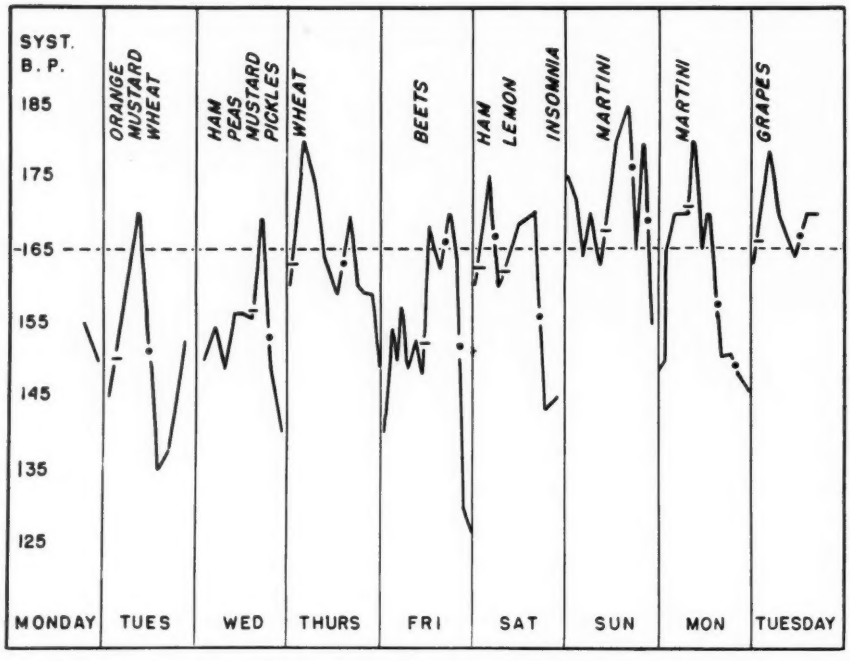

Chart 1.—Blood pressure readings during preliminary period of observation.

but indeed was usually followed by a lowering of blood pressure. On the contrary, Martini cocktails consistently caused an increase. This suggests the possibility that specific sensitization to constituents of certain alcoholic beverages may be responsible for hypertension although the same person may not experience blood pressure increases following the ingestion of other alcoholic beverages. The ingestion of Scotch highballs is indicated on the curve of systolic pressures by breaks with dots.

It was observed during this study that not only foods but emotional states influenced the blood pressure level. Insomnia on Saturday was followed by a general increase in pressure which persisted through Sunday, but it disappeared on Monday. The environment chosen for this study was almost ideal since it was made during a vacation cruise

during which neither the patient nor the examiner had any responsibilities for navigation, etc. The weather was good throughout, and the situation was ideal for rest and relaxation. On the last day, Tuesday, port was reached, contact with affairs was reestablished, and it will be seen that the general trend of the blood pressure was higher on this day.

Table I indicates those foods to which this patient had been found allergic at one or another of the four series of skin testing, or by

TABLE I

FOODS THAT HAVE GIVEN POSITIVE REACTIONS AT ONE TIME OR ANOTHER	POSITIVE BY SKIN TEST				POSITIVE BY LEUKOPENIC INDEX		POS. BY BLOOD PRESSURE
	1930	1933	1935	1936	1935	1936	1936
Apple	**	**		**			
Banana	**	**		**			
Bean	**	**		**			
Beet				**		**	**
Buckwheat			**				
Cauliflower				**			
Carrot		**		**			
Celery	**	**		**			
Chicken		**					
Chocolate	**	**					
Clam				**			
Cocoanut				**			
Coffee			**		**		
Corn			**				
Crayfish				**			
Cucumber	**	**		**			
Ginger							
Grape						**	**
Grapefruit				**			
Ham						**	**
Lemon				**			
Martini							**
Melons	**	**		**			
Milk	**					**	
Mustard			**	**			**
Onion				**			
Orange				**			**
Oyster				**			
Pea	**	**		**			**
Peach			**				
Peanut	**	**		**			
Pear	**	**		**			
Pepper (black)				**			
Pork				**			
Raspberry	**	**	**	**			
Rice		**					
Sardine				**			
Shad				**			
Shrimp				**			
Sole				**			
Spinach				**			
Sweet potato		**		**			
Strawberry	**	**	**	**			
Tea		**					
Tomato	**	**					
Turnip				**			
Walnut			**	**			
Wheat				**	**	**	**

leukopenic index; and the foods following the ingestion of which, pressor responses were observed. It should be noted that an increase in blood pressure was observed only after the ingestion of foods which had been positive by skin test or leukopenic index or both. This is a point of considerable importance in this study since it gives objective confirmatory evidence of the allergic nature of the pressor responses.

At the termination of this intensive study, the patient was placed upon a diet consisting of foods to which he had never given positive skin reactions, positive leukopenic responses, and foods whose ingestion during the period of observation had not been followed by an increase in blood pressure. From August, 1936, until May, 1937, except for one

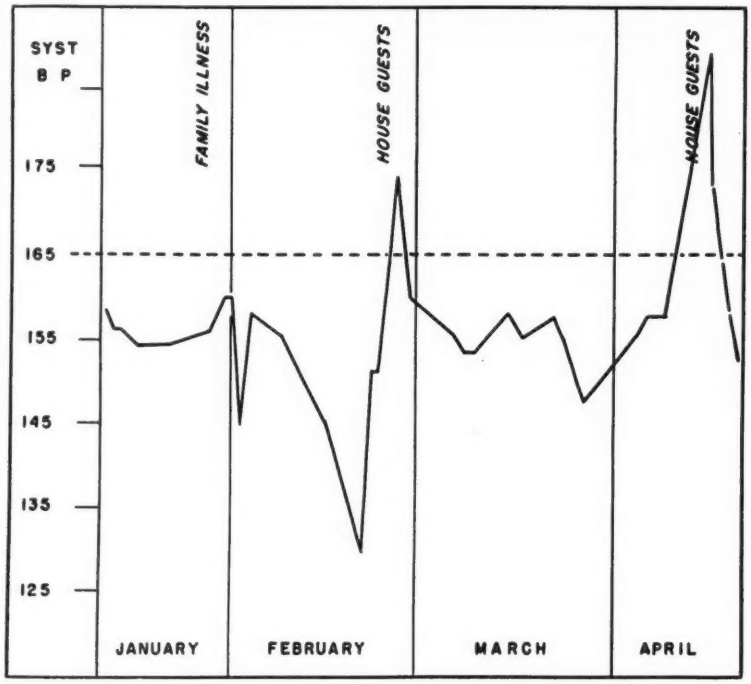

Chart 2.—Blood pressure range during dietary restrictions.

food spree the patient has remained on this diet, which includes Scotch whiskey, but not gin or any other alcoholic beverage. He spent from September until January on an isolated country estate, conducive to physical and mental relaxation. During this period blood pressure determinations were made twice weekly. The systolic pressure ranged from 142 to 148 mm., exceeded 150 only on one occasion when an emotional upset was the obvious direct excitant.

From January 13 to April 21, 1937, the patient resumed his more active customary routine. During this interval blood pressure determinations were made twice weekly or oftener (Chart 2). It will be seen that the systolic pressure remained below 160 mm. much more

consistently than during the eight days of preliminary survey. Furthermore, with one exception pressor episodes followed, not the ingestion of proved allergenic foods, but situations in which the patient was naturally placed under a greater mental strain. In the discussion of Chart 1 two such episodes were described (Sunday and Tuesday), but there were many other days in which a hypertensive response above 165 followed the ingestion of allergenic foods. It will be seen from Chart 2 that these latter have been eliminated, due presumably to the dietetic restrictions.

The one exception just mentioned is represented by the last and highest peak on Chart 2. This was a period when the patient was doing much entertaining. Also for forty-eight hours preceding the pressure determination he had broken his diet for the only time in the entire period of study. During those two days he was on a food spree, eating nearly all of the prohibited foods.

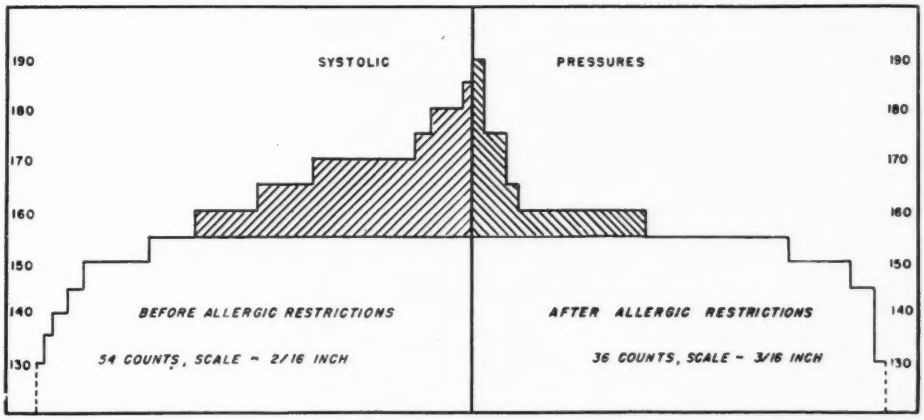

Chart 3.—A comparison of the systolic pressure range during the eight days of study in August, 1936, and that during the four months of 1937, detailed in Chart 2. Since there are 54 determinations in the first period and 46 in the second, the scale in the latter is slightly larger to provide base lines of equal length.

Chart 2 shows a general systolic blood pressure range in the neighborhood of 155 mm. The diastolic pressure during this period did not fall notably. It ranged from a low of 102 to a high 108 mm., following in general the deviations of the systolic pressure. Even when on one occasion the systolic fell to 130, the diastolic remained at 102 mm.

Chart 3 presents a comparison of the systolic range during the eight days of study in August, 1936, with the determinations during the four months of 1937, as detailed in Chart 2. Since there were 54 counts in the first period and but 46 in the second, the scale in the second group is slightly larger to provide base lines of equal length. The comparison, before and after, would be statistically more accurate if the same number of blood pressure determinations had been made in each grouping. However, this is a factor which we could not control and

conclusions must, therefore, be based on the material available. Pressure ratings are recorded to the nearest five millimeter variation. It becomes apparent from Chart 3 that, below 155 mm. systolic, there is no notable change in the frequency of the various readings. There has been no notable lowering of the basic hypertension. Higher pressure on the other hand shows decidedly diminished frequency which becomes especially notable above 160 mm. In this latter category there were only four peaks after allergic restrictions as contrasted with 27 before the institution of such restrictions. Fifty per cent of the readings before restriction were above 160 mm. as contrasted with 8.7 per cent after.

The evidence presented so far in the study of this case suggests very strongly that, given a person with a tendency toward essential hypertension, who is at the same time allergic to certain foods, avoidance of the latter will prevent many pressor episodes which appear to have been due to contact with the allergenic substances. At the same time the basic hypertensive tendency persisted in this case, and emotional or mental excitants are still able to determine temporary pressor responses. Furthermore, the continued use of alcohol, entirely aside from the allergic factor, will probably serve as a hypertensive excitant. In this particular case one would not anticipate a complete return to normal pressure since the physical examination showed that there were already some organic changes in the small vessels, as indicated by low grade retinal periarterial streaking with slight arteriovenous compression. Nothing further pertinent to the present discussion was found in the physical examination or laboratory studies. There was no evidence of arteriosclerotic involvement of the large vessels. Kidney function appeared normal.

EXPERIMENTAL

If the hypertensive response in this patient was truly due to the ingestion of allergenic foods, one should be able to demonstrate a similar type of reaction among other allergic persons. Three methods of approach to this study appeared logical. (A) One might select a series of cases of essential hypertension, studying them for evidence of allergy and subsequently observing blood pressure response following exposure to the allergens. This would be a duplication and extension of the work just reported and that described by Waldbott. (B) One might study a series of allergies, separating out those with hypertension, and observing the latter to see whether the ingestion of specified allergenic foods will be followed by a hypertensive response. Either of these procedures would provide information concerning allergens as hypertensive excitants in persons with an antecedent hypertensive tendency. (C) One might study a series of allergic individuals with normal blood pressure with the object of determining whether some of these might re-

spond to contact with allergens specific for them, with an increase in blood pressure. There is a slight difference between the first two and the third possibility, since positive findings in A and B would implicate allergy as a secondary factor, while positive findings in C might suggest the possibility of allergy as being a primary cause. Positive findings would not prove that allergy is primary in such cases, since the possibility still exists of a hypertensive predisposition that has not yet become manifest, but they would certainly indicate the importance of allergens as very early excitants and, as a corollary, the importance of their early avoidance. The writers have undertaken a study of the third of these propositions. Our findings, although in no way con-

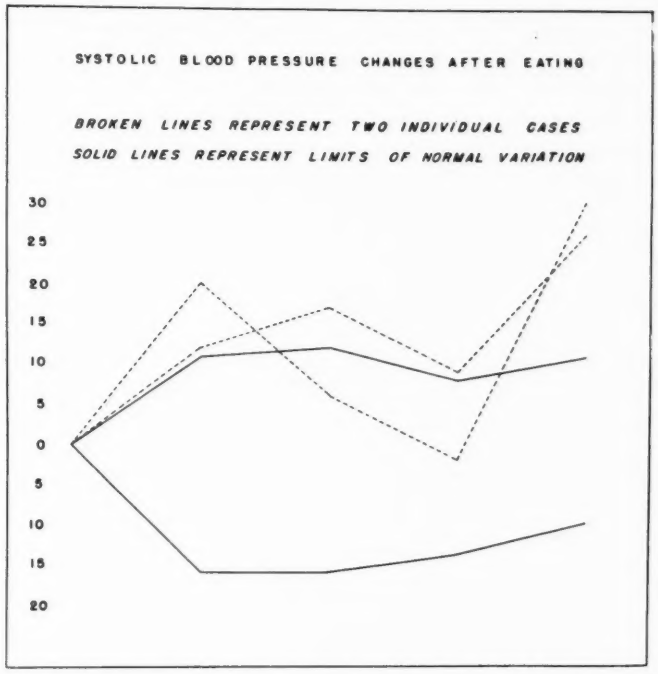

Chart 4.—Serial systolic pressure curves following the injestion of allergenic foods.

clusive, are most suggestive, and indicate the desirability of further study of all three propositions. In this study, investigations were limited to food allergens.

Method.—Eighty-one allergic persons were studied. The patient reported to the office at 9 A.M. without breakfast. He was assigned a private room on the third floor of the clinic building, with no other patients on the floor, and with no one entering the room during the period of study other than the physician and the technician. Throughout the period of observation, including the period of eating the test food, the patient reclined at ease on a comfortable studio couch. As a rule several such tests were performed on each individual and the

factor of apprehension was eliminated. Without exception the patient enjoyed the procedure and considered it a pleasant rest.

Blood pressure determinations were made graphically with the Tycos Sphygmotonograph. After a rest interval, two blood pressure determinations were made at fifteen minute intervals. The patient then ingested the test food. Following this, four determinations were made at half hour intervals. Blood pressure changes during the two hours after the ingestion of the test food were recorded graphically. Leukopenic index studies were made synchronously, the blood for white count being obtained each time after the blood pressure determination.

Findings.—In no case did the diastolic pressure vary more than 15 mm. including up and down from the fasting rest level. In 90 per cent the variation was no more than 10 mm. There was rather wider variation in the systolic pressure. This is shown in Chart 4 in which the full lines enclose the extremes of all variations in postprandial blood pressure except for two individual cases indicated by the dotted lines. It will be seen that with the exception of these two cases the highest upward variation after feeding, with the patient resting, was 15 mm. Hg.

This chart includes tracings upon allergic patients tested with foods to which they were not sensitized and serving as controls, as well as allergic persons tested with foods to which they were known to be sensitized. Ninety determinations were made, using 24 known allergenic foods and 66 nonallergenic controls. Quite a variety of foods were used including milk, egg, wheat, pork, rice, Coca Cola, apple, asparagus, beef, chocolate, chicken, cabbage, coffee, orange, tea, Irish potato, corn, oatmeal, tomato, green peas, veal, and onion.

The blood pressure responses were grouped according to whether the patient was nonallergic to the test food, mildly sensitized, or very strongly sensitized. All three groups showed variations of similar degree up and down, entirely similar to that indicated in the "normal" area in Chart 4. With the exception of the two cases indicated by the dotted lines, there was no difference in the character of the blood pressure response to allergenic or nonallergenic foods.

Our present interest is in the two exceptional cases (Table II).

CASE REPORT

Mr. N., aged twenty-four years, had had eczema of two years' duration. He was tested in the manner described, with three foods, milk, wheat, and egg. Scratch and endermal skin tests with milk and wheat had been negative while scratch reaction to ovomucoid was two-plus. Endermal reaction to whole egg was three-plus. Leukopenic index studies were made along with the blood pressure determinations. A drop of over 1,000 in the white count, from the lower of the two fasting counts is interpreted as a mildly positive leukopenic index, indicative of sensitization to the food under study. A drop of over 2,000 is strongly positive. It will be seen from

the table that the leukopenic responses to milk and wheat were negative. At the same time there was no variation in blood pressure beyond the normal average. On the other hand, eggs which had been skin test positive produced a drop of 2,200 in the white count, while the systolic pressure rose 20 mm. on one determination, 30 on another. Variations in the diastolic pressure were in the same direction. This patient was allergic to egg and experienced a rise in pressure following its ingestion. He was not allergic to milk or wheat, and the blood pressure response remained normal. The patient eliminated egg from his diet, following which within a period of ten days, his eczema improved by about 60 per cent.

The second case, Mrs. J., aged forty-four years, had had urticaria of ten years' duration. She was found allergic to a number of foods, including chicken, and it was also found that she suffered from physical allergy, heat and effort producing attacks of urticaria. She was placed on allergic dietary restrictions and was placed upon a routine of acclimatization to increasing degrees of heat. At the end of six weeks she returned, entirely free from symptoms. Whereas a tub bath at 98° or 100° F. had for years produced generalized urticaria, she could now tolerate water at 110° without reaction.

TABLE II

NAME	MR. M.			MRS. J.		
Food Tested	Milk	Wheat	Eggs	Eggs	Asparagus	Chicken
Skin Tests						
Scratch	neg.	neg.	++	neg.	neg.	
Endermal	neg.	neg.		neg.	+++	++
White Blood Counts at Rest						
Fasting	5450	6650	7025	6075	5050	5755
Fasting	5525	6000	6875	5525	4625	3225
30 min. after eating	5525	6550	4900	5750	4750	4975
60 min. after eating	5625	8175	4600	5950	4800	4825
90 min. after eating	5125	6500	4900	5375	4825	5775
120 min. after eating	5875	6000	4925	6475	5060	3825
Blood Pressures at Rest Mm. Hg						
Fasting	127/80	114/70	122/77	112/73	125/75	120/80
Fasting	126/77	114/73	122/78	125/77	128/76	121/85
30 min. after eating	121/84	112/75	142/83	122/74	130/82	132/85
60 min. after eating	127/86	121/72	128/75	103/66	135/87	137/87
90 min. after eating	125/90	129/76	127/78	126/72	124/77	129/78
120 min. after eating	137/76	115/76	152/79	128/71	120/76	146/95

One of the foods which she had eliminated was chicken. Endermal skin test had been two-plus. After six weeks on her diet, and at a time when she was free from symptoms, she was tested by the ingestion of chicken. Leukopenic index and blood pressure determinations were made. The former was negative according to the standards described above, although it should be noted that with low white counts such as the unusual fasting 3,225 recorded in her case, we have found that the leukopenic index is not as reliable. The interesting point is that her blood pressure rose 25 mm. above the fasting level; that there was a corresponding increase in diastolic pressure; and that a few hours after completion of the test she experienced the first attack of urticaria which she had had in four weeks.

She had been tested in a similar way with eggs and asparagus. Eggs were negative by skin test and leukopenic index, and there was no abnormal increase in blood pressure. Asparagus had been positive to endermal skin test, but the leukopenic index was negative and there was no abnormal rise in blood pressure.

Our experience has been that a positive skin reaction may indicate present difficulty, past trouble or potential future trouble, but that a positive leukopenic index usually indicates present trouble rather than past or future. The interpretation of the asparagus reaction would, therefore, be that this patient shows evidence of allergy to asparagus but that asparagus at present does not cause symptoms. She is not allergic to egg. The leukopenic reaction to chicken is unfortunately not characteristic. This may be explained on two points. The low fasting white count interferes with the accuracy of the determination. Symptoms appeared several hours after the test and it is possible that if we had had an opportunity to repeat the white count at that time it might have been found distinctly lower. We have found that with the leukopenic index as with the scratch skin reaction some reactions are delayed. Certainly her clinical reaction was delayed.

This experimental evidence would indicate that the customary blood pressure response to the ingestion of allergenic foods is similar to that following the ingestion of nonallergenic foods and is definitely not in the nature of a pressor response. In 2 among 24 positive cases, however, pressor response was observed. In these two cases it occurred after the ingestion of specific allergenic excitants but not after the ingestion of foods to which they were not sensitized.

Neither of the two cases studied shows as yet a hypertensive predisposition, nor were we able to obtain a definite family history. However, this was unsatisfactory since both parents of the first patient were living and not beyond middle age, and they knew nothing of other more remote members of the family. The mother of the second patient died following an operation, and the father died from pneumonia. One brother did die of Bright's disease. Special interest, however, does attach to the second case in view of her indubitable hypersensitiveness to heat. Kaufmann[10] has observed that in essential hypertension sensitiveness to heat is an outstanding feature of the history.

Neither case showed an extreme hypertensive response, but the trends are obvious. In the case of Mr. M., expecially, the pressor response exceeded the generally accepted upper limit of normal (145 mm.).

DISCUSSION

The three most characteristic responses both in experimental anaphylaxis and clinical allergy are (1) smooth muscle spasm, (2) serous exudation associated with increased capillary permeability, and (3) eosinophilia.

In view of the widespread distribution of smooth muscle in the vasculature, one would be justified in anticipating a pressor response in the allergic reaction. On the contrary, anaphylactic shock, both clinical and experimental, is characterized by a pronounced fall in blood pres-

sure. Shock is, however, an extreme manifestation. The fall in pressure appears to be due to loss of fluid from the vessels consequent on increased capillary permeability. It is of especial interest in connection with the present discussion that in experimental anaphylactic shock in the rabbit and cat at least, there is a temporary rise in blood pressure, followed by fall. It seems logical to interpret this as being due, first to smooth muscle contraction in the smaller vessels, which is later counteracted by loss of fluid due to capillary hyperpermeability. In a severe reaction the pressor response is masked by the phenomena of shock. In the absence of shock, the hypertensive response should be more clearly demarcated.

If this be true, the question will be raised as to why a hypertensive response does not occur regularly in allergy.

Doerr, likewise Coca, has presented the theory of the shock organ or shock tissue in allergy. Certain tissues of the body may be locally responsive in the allergic reaction. The commonest of these are the skin, the nasal mucosa, the bronchi, and the intestinal tract. Experimentally the uterine musculature is also a shock tissue, as is demonstrated in the Dale phenomenon. There is evidence that either as a result of local tissue sensitization or some other as yet incompletely understood process, at times only one shock tissue may be responsive. Thus the hay fever patient reacts only in the nose. The allergic with urticaria or eczema reacts only in the skin. Sometimes two or more shock tissues respond simultaneously. The most highly responsive shock tissue in the guinea pig is that of the bronchial musculature while that of the rabbit is that of the vasculature of the pulmonary circulation. In the dog the most highly responsive shock tissue appears to be that of the portal circulation. There is evidence that the blood vessels of the kidney may respond to allergic excitants, with spasm.

In the absence of local sensitization in the shock organ, or of tendency to local response, one would anticipate no local response. The experimental evidence cited above suggests that smooth muscle of the vascular system may at times be an allergic shock tissue. Only in those cases in which the vascular musculature is locally sensitized or is an allergic shock organ might one anticipate the finding of allergic hypertension. Our observations would indicate that this occurs in a small proportion of allergic individuals.

Essential hypertension is a disease the etiology of which is, in last analysis, still unknown. The observations herein reported suggest that one contributory factor may be specific sensitization, provided the individual is allergic and, further, provided the vascular musculature happens to be a shock tissue in the individual case.

The existence of an allergic state would not be alone sufficient to produce essential hypertension. The hypertensive predisposition must also be present. In the presence of the latter, the former may determine

pressor episodes. Whether this is through the mechanism of the vasculature as a shock tissue based upon a local chemical or colloid reaction or mediated through a reflex response can be determined only after more is learned of the mechanism of essential hypertension.

The evidence obtained from the study of the first case as illustrated in Charts 1 to 3 would indicate that the avoidance of allergenic excitants, although diminishing the hypertensive response, does not eliminate the basic tendency nor does it bring the blood pressure back entirely to normal. This is also observed in Waldbott's case in whom, although the systolic pressure fell from a high of 212 mm. to around 150 mm., where it remained fairly consistently for over two years, during this same interval the diastolic pressure which had fallen from 115 mm. to 92 mm. gradually climbed until after two years it was ranging around 109 mm. This would suggest a gradual progression of the basic pathologic process.

More recent study of the first case studied, however, suggests that in a case with essential hypertension in which there is an allergic factor such as food allergy, the possibility exists of more satisfactory control of the nonallergic factors provided the allergic factors are eliminated. Chart 2 shows the patient's systolic response from January 13 to April 21, 1937. The diastolic range during this period was from 102 mm. to 108 mm. As we have previously stated, both systolic and diastolic pressures were decidedly lower than this from September to January when he was resting in the country. In a final period from April 21 to May 18, 1937, he continued at his same occupation and in the same location as during the period January to April. He not only remained on his dietary restrictions but also took all reasonable precautions to secure adequate rest, freedom from vexation, etc. During this last four weeks of observation the blood pressure was taken at least twice weekly and dropped definitely to average around 148 mm. systolic, 95 diastolic.

SUMMARY

A man with essential hypertension who was at the same time allergic to a number of foods was found to exhibit pressor responses following the ingestion of substances to which he was allergic. Allergic dietary restrictions resulted in the disappearance of hypertensive pressure peaks except for a few which could be traced to mental or emotional strain and on one occasion to a break in the diet. The hypertensive tendency persisted, however, since neither systolic nor diastolic pressure returned completely to normal. This was especially evident with the diastolic pressure. The continued use of alcohol is probably one deterrent to complete recovery.

When, in addition to allergic eliminations, the patient avoided strenuous mental and physical activities, both systolic and diastolic pressures fell further, to near the upper limits of normal.

In a series of 24 individuals with food allergy, 2, not including the case just described, responded to the ingestion of foods to which they were known to be reactive, with an increase in systolic and diastolic pressures. The remainder of the series exhibited no such response. It is noteworthy that one of the two was hypersensitive to heat, a phenomenon which has been described as common in hypertensives.

Evidence is presented which suggests that a person with hypertensive predisposition (nonallergic) may, if at the same time he happens to be hypersensitive to foods, experience pressor episodes following the ingestion of foods to which he is sensitized.

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201 W. FRANKLIN STREET

BONE SCORINGS IN NORMAL AND ALLERGIC CHILDREN*

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TRANSVERSE linear markings situated proximal to the epiphyseal line in growing long bones have been recognized since the early days of radiology, and it has hitherto been the accepted opinion that these transverse lines were due either to periods of variation in growth or were secondary to starvation, dehydration, acute infections of the respiratory, urogenital or alimentary tracts, or to a deficiency disease such as scurvy.[1]

Köhler[2] in his "Röntgenology" described delays in bone growth occurring as the result of infectious diseases, and also described transverse bands occurring as the result of continued deposition of calcium salts in the cartilaginous ground substance after growth in length or cartilaginous proliferation has stopped.[3] He stated that these bands continued obstinately for years until finally they were completely absorbed. Köhler further described "light transverse lines" parallel to one another in the shadow of the spongiosa of the distal end of the tibia, and stated that they were of no particular pathologic importance. He simply stated that one is dealing with an irregular intermittent ossification, dating from youth and caused by various forms of chronic disease.

Phemister[4] described bands of increased density at points where growth was occurring when small doses of yellow phosphorus were administered over a period of time, but these bands failed to appear when yellow phosphorus was omitted. These lines gradually lost their density over a period of years.

Park[5] has shown that very thin discs of enlarged, densely packed, and transversely arranged trabeculae occur in the newborn which appear radiographically as lines in infants and in older children who have suffered acute or chronic illness. He also demonstrated such scorings in the bones of rats that were starved for several days. Park, Vogt[6] and Caffey[7] have described very dense lines in the bones of growing children suffering from lead poisoning. Caffey[8] has also recently described dense bands occurring in growing long bones in utero, coincident with bismuth therapy of syphilis in the mother.

The existence of bone scorings in allergic children was brought to the attention of this Society at its meeting in New York City, December, 1936, by Dr. T. Wingate Todd. At that meeting he pointed out the significance of certain transverse markings in the bones of growing chil-

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dren, and stated that he believed they were the result of allergic stimuli. In that presentation, as yet unpublished, Dr. Todd expressed the opinion that at least fifty per cent of the children studied in the Brush Foundation, at Western Reserve University, Cleveland, were allergic, and he based this opinion on the presence of bone scorings. He felt that he could estimate the period of time elapsing between allergic attacks, which he definitely thought left their mark on the skeletal structure in the form of transverse striations or "bone scorings." Dr. Todd pointed out that these scorings were most marked in children of preschool age and tended to disappear as the child grew older. He stated further that certain bones are most commonly affected; the lower tibia bearing the brunt of dietetic disorders and the lower radius, lower femur and upper tibia being more often scored by the effects of the exanthemata.

Eliot, Souther and Park[10] offer a rather extensive study concerning the significance of transverse lines with especial reference to rickets. In their studies they demonstrated that transverse dense lines are frequently found to alternate with zones of apparent rarefaction, and they pointed out that it is difficult to determine whether these zones are really due to true rarefaction, or whether they are the result of contrast with the dense lines above and below. Both the transverse dense lines and the zones of apparent or real rarefaction are exactly parallel to the end of the shaft of the bone in which they occur. According to their studies, when these dense transverse lines and the alternating zones of rarefaction develop, they occur simultaneously at the growth levels of all bones, even the ribs, but the more delicate formations in the small bones are not seen ordinarily, due to the overlying soft tissues. If the bones, such as the ribs, are studied radiographically after the removal of the overlying soft tissues, the transverse dense lines and the alternating lighter zones are clearly demonstrated.

The diagnostic importance of Todd's observations was apparent to both the allergist and the radiologist and prompted this study. For our purposes a group of 17 known allergic children were studied. Four were infants who had not yet walked, and the remaining 13 were allergic children who had been followed for varying lengths of time in the Pediatric Allergy Clinic at Post Graduate Hospital.

As our control group, seven children of varying age whose family histories had been carefully checked for the presence of allergy and in whom no clinical evidence of allergy had made itself apparent were studied. In addition six children taken from the feeding clinic, suffering from rickets, were also studied.

Todd declared that during the period of freedom from allergic attacks no bone scorings would be visible. We, therefore, included in our group two private cases which had been carefully followed for a period of over two years with complete enjoyment of freedom of symptoms of asthma or any other form of allergy.

TECHNIQUE

The radiographic technique used in the study of the control group, the group of known allergic children, and the group from the feeding clinic who were suffering from rickets, was identical with that used by

Fig. 1.—J. P., aged six years (Case 1). Scorings present in both radius and tibia—more marked in tibia.

Todd in his work at the Brush Foundation, and which he was kind enough to explain to us personally. That technique was followed in minute detail so that errors due to technical differences would be obviated.

CASE 1.—J. P., aged six years (Fig. 1): asthma began at age of nine months. Infectious diseases—pertussis, measles, mumps, and chickenpox. Mantoux negative. Skin tests—marked to dust and moderate to rice and barley; these tests were confirmed by clinical feeding.

Radiograph of chest—"Marked hilus, root branch and central bronchial thickening with involvement of the interlobar septums, especially on the right side."

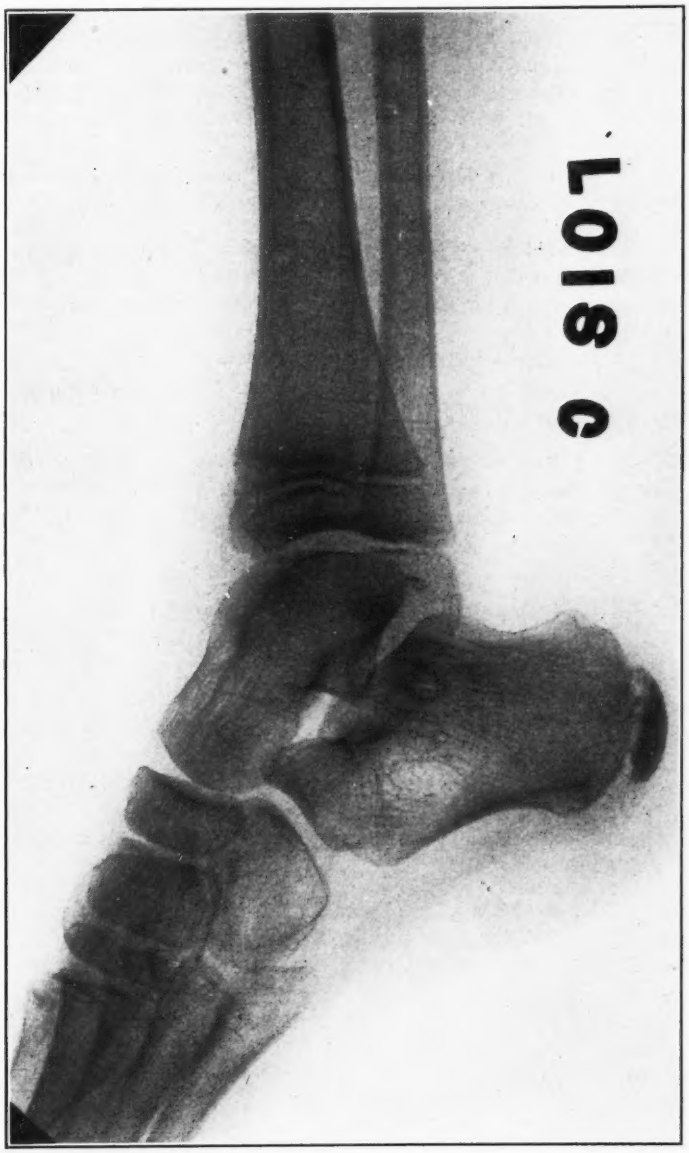

Fig. 2.—L. C., aged seven years (Case 2). Both distinct and faint scorings in tibia and fibula, and in the radius. More marked in tibia and fibula.

Radiograph of nasal accessory sinuses—"Involvement of left antrum and ethmoids."

The radiographs of the left ankle and wrist showed scorings present in both the radius and tibia—more marked in the tibia. Epiphyseal growth normal.

CASE 2.—L. C., aged seven years (Fig. 2): no acute infectious diseases. Eczema since age of two years, worse in winter than in summer. Wheat made eczema definitely worse. Physical findings showed distribution to be characteristic of a neurodermatitis. Skin tests and clinical feedings showed definite sensitivity to wheat. BMR—minus 20.

The radiographs of the left ankle and wrist showed distinct and faint scorings in the tibia and fibula, and in the radius; more marked in the tibia and fibula.

CASE 3.—H. R., aged three years: eczema since age of three months; asthma since age of two years. Pertussis at age of two months. No other infectious disease. Food tests which were checked by clinical feeding showed hypersensitivity to egg, wheat, barley, and white potato. There was also sensitivity to house dust and ragweed.

The radiographs of the left ankle and wrist showed both marked and faint scorings in tibia, and faint scorings in radius.

CASE 4.—C. S., aged five years: bronchial asthma began at age of two years. Admitted to hospital twice with bronchial asthma and pneumonia. Sensitivity to ragweed, orrit root, cat and rabbit epithelium, and white potato. Mantoux negative.

Radiograph of nasal accessory sinuses showed "paranasal sinus infection."

The radiographs of the left ankle and wrist showed very faint scorings in the tibia, and no scorings in the radius and ulna. The scorings were not consistent with the severity of the allergy.

CASE 5.—J. S., aged six years: bronchial asthma since age of three years. Asthma occurred chiefly after colds. One sister had asthma. Pertussis at age of four years. Skin tests negative.

Radiograph of the nasal accessory sinuses showed "paranasal sinus disease."

The radiographs of the left ankle and wrist showed marked scorings in the tibia and radius.

CASE 6.—A. J., aged seven years: eczema since age of one month. Bronchial asthma since age of one year. Skin tests showed marked sensitivity to house dust, horse dander, horse serum, cat and dog epithelium, and feathers. Admitted to hospital on two occasions with bronchopneumonia. The last attack of bronchopneumonia was in September, 1936, at which time abscessed molars and incisors were extracted.

Radiograph of the nasal accessory sinuses showed "slight infiltration of both ethmoids."

The radiographs of the left ankle and wrist showed many marked scorings in the tibia, and faint scorings in the radius.

CASE 7.—R. S., aged six years: bronchial asthma since the age of one year. The attacks followed colds. Grandmother had hay fever. No history of any infectious disease. Tests showed sensitivity to ragweed, timothy, house dust, and feathers. Mantoux negative.

Radiograph of the nasal accessory sinuses showed "slight membranous infiltration of the right ethmoids and the right antrum."

Radiograph of the chest showed "accentuated bronchovascular markings."

The radiographs of the left ankle and wrist showed faint scorings in the tibia, and barely perceptible scorings in the radius.

CASE 8.—F. W., aged four and one-half years: bronchial asthma since age of four years. Food sensitivity to eggs and milk. Father and grandfather had hay fever. All skin tests completely negative. Child had scarlet fever.

The radiographs of the left ankle and wrist showed faint scorings in the tibia, and barely perceptible scorings in the radius.

CASE 9.—E. M., aged ten and one-half years: no history of bronchial asthma. In infancy there was definite food sensitivity to eggs and milk. Skin tests showed definite sensitivity to wheat, silk, and ragweed. Has had pertussis, measles, mumps, and chickenpox.

The radiographs of the left ankle and wrist showed faint scorings in the tibia and the radius.

CASE 10.—S. J., aged twelve and one-half years: no history of bronchial asthma. In infancy there was sensitivity to eggs. Skin tests showed sensitivity to ragweed. Has had pertussis, measles, mumps and chickenpox.

The radiographs of the left ankle and wrist showed no scorings.

CASE 11.—M. M., aged five and one-half years: bronchial asthma since the age of three years, infectious in type. The attacks usually followed a cold. The asthmatic attacks had been fairly frequent. Severe pertussis at age of three years. Skin tests showed definite sensitivity to house dust.

Radiographs of the nasal accessory sinuses had shown pansinusitis at intervals.

The radiographs of the left ankle and wrist showed scorings of moderate degree in both the tibia and radius.

CASE 12.—J. B., aged ten years: bronchial asthma since age of six years. Father and grandmother also had bronchial asthma. No history of the exanthemata. Skin tests were negative. Both antra were dark on transillumination. Autogenous vaccine from antral washings produced beneficial effect on the asthma, and there had been no attacks of asthma for the past three years.

The radiographs of the left ankle and wrist showed marked scorings of the tibia, and faint scorings of the radius.

CASE 13.—L. G., aged ten years (Fig. 3): bronchial asthma started at the age of six months. Treatment was started at the age of seven years, and there had been no attacks of asthma for the past three years. All tests negative.

Radiographs of the nasal accessory sinuses showed "haziness of the ethmoids."

Radiographs of the chest showed "increased prominence of the bronchovascular markings."

Radiographs of the left ankle and wrist showed many moderate scorings in the tibia, and faint scorings in the radius. Some of the scorings had certainly occurred during the past three years.

CASE 14.—C. S., aged five and one-half months: history: eczema.

Radiographs of the left ankle and wrist showed no bone changes other than those incident to rickets.

CASE 15.—K. McE., aged seven and one-half months: infantile eczema first appeared on face at age of five weeks. Skin tests showed definite sensitivity to barley, chicken, and pork.

Radiographs of the left ankle and wrist showed no bone changes other than those due to rickets.

CASE 16.—C. A., aged fourteen months (Fig. 4): this child attended the feeding clinic. A nasopharyngitis was present.

Radiographs of the left ankle and wrist showed faint scorings in the radius, and less marked scorings in the tibia. The other bone changes were those incident to rickets.

CASE 17.—J. B., aged five and one-half months: this child was a feeding problem —also had an asthmatic bronchitis. Mantoux negative.

Radiographs of the chest showed "infiltration of soft tissues in lower cervical retro-tracheal area."

Radiographs of the left ankle and wrist showed very faint scorings in the tibia, with no evidence of scorings in the radius. Other bone changes are indicative of a quiescent rickets.

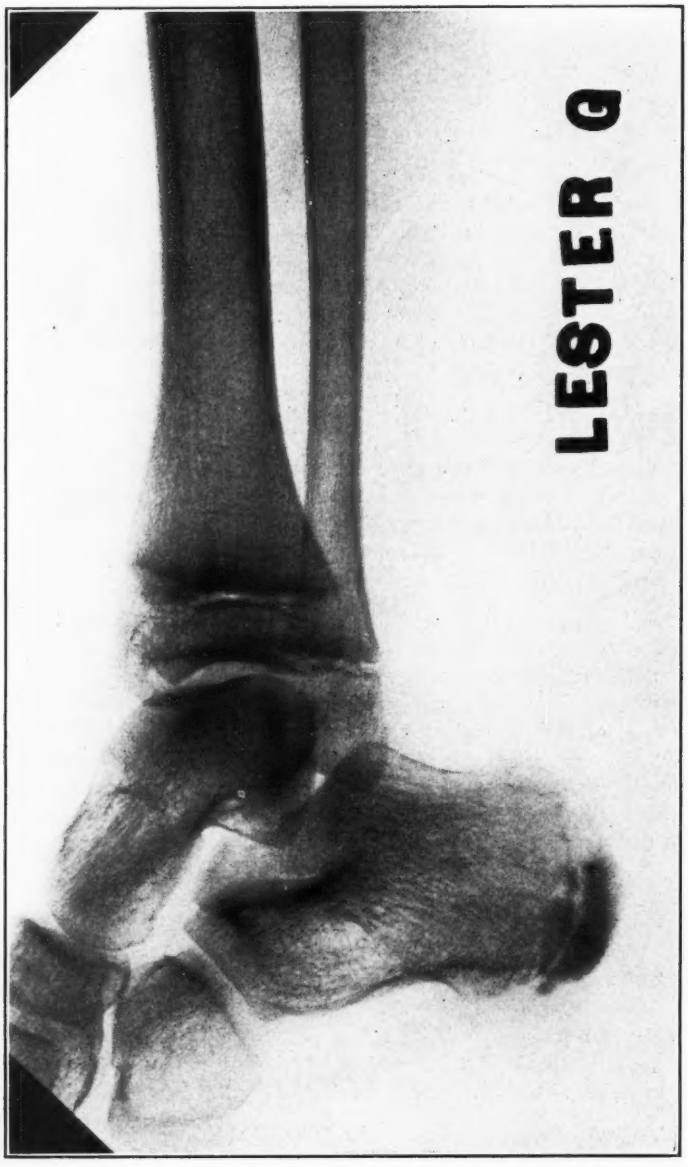

Fig. 3.—L. G., aged ten years (Case 13). No attacks of asthma for past three years. Scorings present in tibia and radius.

CASE 18.—S. P., aged sixteen months: patient was admitted to the clinic with a diagnosis of upper respiratory infection and bronchitis. All skin tests negative.

Radiographs of the chest showed "moderate degree of root thickening and pulmonary hypervascularization. . . ."

Radiographs of the nasal accessory sinuses showed "pansinusitis."

Radiographs of the left ankle and wrist showed only bone changes to be those incident to rickets. No scorings.

CASE 19.—R. P., aged eleven months: this patient attended the Nose and Throat Clinic through October, November, and December, 1936, and the Pediatric Clinic

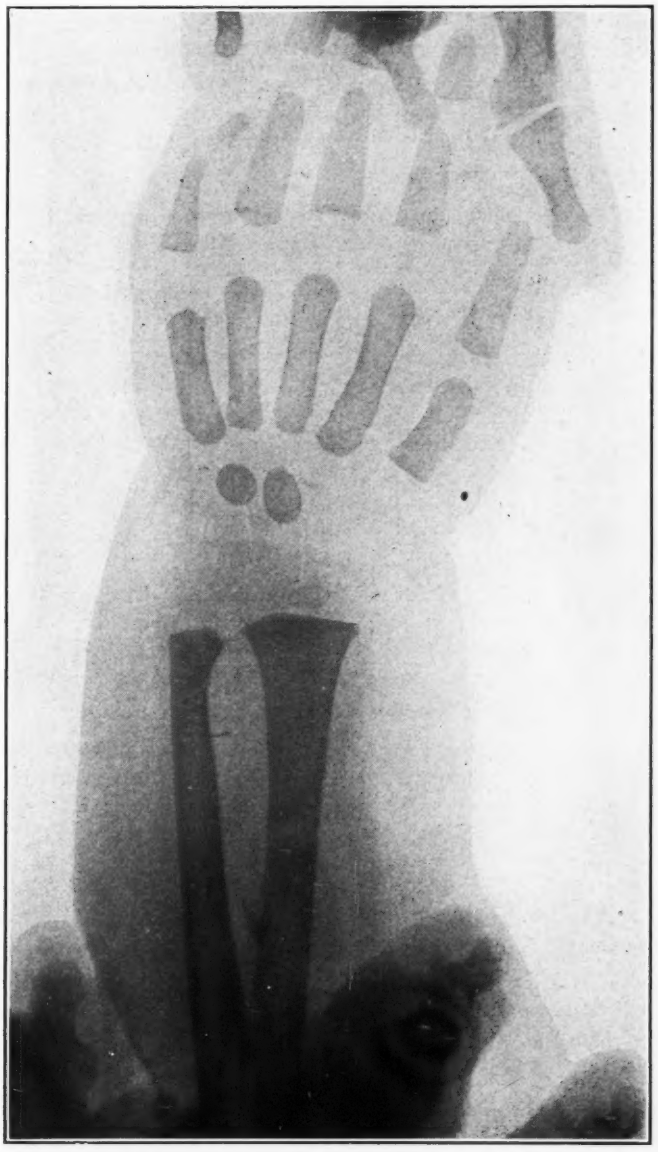

Fig. 4.—C. A., aged fourteen months (Case 16). Feeding problem. Scorings present in radius and tibia. More marked in radius.

from May, 1936, to March, 1937. Had bronchopneumonia in November, 1936, and mastoidectomy on December 3, 1936. Mantoux negative.

Radiographs of the left ankle and wrist showed definite scoring (one line) in the tibia and the radius. Other changes were those incident to quiescent rickets.

CASE 20.—R. T., aged nine and one-half months: attended feeding clinic for diet regulation.

Radiographs of the left ankle and wrist showed questionable scorings in the tibia and ulna. Other bone changes were those incident to quiescent rickets.

CASE 21.—R. M., aged five and one-half months: eczema was first noticed on head at age of six weeks.

Radiographs of the left ankle and wrist showed no bone scorings.

CASE 22.—N. G., aged nine months: attended feeding clinic for treatment of fermentive diarrhea.

Radiographs of the left ankle and wrist showed no bone scorings. Other bone changes were those due to quiescent rickets.

CASE 23.—V. LaR., aged six months: patient attended Nose and Throat Clinic for treatment of bilateral otitis media, acute pharyngitis, and rhinitis.

Radiographs of the left ankle and wrist showed very faint bone scorings in the tibia and radius. There were other bone changes due to rickets.

CONTROL GROUP OF NORMAL CHILDREN OF VARYING AGES

CASE 24.—J. M., aged four years and one month: no familial history of allergy. This child was susceptible to common colds, but has improved somewhat since submucous resection and tonsillectomy and adenoidectomy at two and one-half years of age.

Radiographs of the left ankle and wrist showed marked bone scorings in the tibia, and faint bone scorings in the radius.

CASE 25.—J. G., aged five and one-half years: no familial history of allergy. This child was quite susceptible to colds in infancy, but had improved since tonsillectomy and adenoidectomy at age of four years. No signs or symptoms of allergy. Feeding history normal.

Radiographs of the left ankle and wrist showed marked bone scorings in the tibia, and faint bone scorings in the radius.

CASE 26.—G. T., aged four and one-half years: no familial history of allergy. This child has had chickenpox, mumps, and measles; all with uncomplicated recovery. Sauer vaccine given at three years. Had pneumonia at one year of age and at three years and eight months. No colds since tonsillectomy and adenoidectomy one year ago. Never any evidence of allergy.

Radiographs of the left ankle and wrist showed faint but definite bone scorings in the tibia and radius.

CASE 27.—B. A. W., aged five years and ten months: no familial allergic history. This child had pertussis at two and one-half years of age and measles at five and one-half years. Not subject to common cold. No evidence of allergy.

Radiographs of left ankle and wrist showed marked bone scorings in the tibia, and faint bone scorings in the radius.

CASE 28.—J. H., aged two and one-half years: no familial allergic history. No evidence of allergy. Had had occasional cold during past six months. No other diseases. Development had been normal and feeding had been normal. Had had Sauer vaccine.

Radiographs of left ankle and wrist showed marked bone scorings in the tibia, and less marked bone scorings in the radius.

CASE 29.—D. K., aged four years and one month: no familial allergic history. This child had bilateral otitis media at age of two years—paracentesis was done with good recovery. Pertussis at three and one-half years with good recovery. No signs or symptoms of allergy.

Radiographs of the left ankle and wrist showed bone scorings of marked degree in the tibia and radius.

CASE 30.—J. K., aged five years: no familial allergic history. No signs or symptoms of allergy. Bilateral otitis media at three years with good recovery.

Radiographs of left ankle and wrist showed bone scorings of moderate degree in both the radius and ulna.

BONE SCORINGS IN ADULTS

CASE 31.—Miss H. H., aged thirty-two years: patient was an apparently normal woman who presented herself for radiographic examination in search of bone injury.

There were bone scorings of marked degree in both tibiae; the scorings were symmetrically placed in both bones.

CASE 32.—Miss G. V., aged twenty-seven years: patient was a normal woman who presented herself for radiographic examination in search of bone injury.

There was evidence of marked bone scorings in the left tibia.

CASE 33.—Mrs. D. F., aged thirty-seven years: the patient was examined for evidence of bone disease.

Bone scorings of moderate degree were present in both tibiae.

DISCUSSION

Harris described an experiment in which Hunter bored two small holes in the shaft of a long bone of a living animal. Into these holes were inserted two small lead shot, after which the distance between the two pieces of shot was carefully measured. The animal was allowed to live for some time, after which it was killed and the distance between the two pieces of shot was carefully measured. As Hunter had expected, the distance had remained unchanged. Harris confirmed this finding to prove that interstitial growth in length does not take place in bone, and that all increase in length occurred at the epiphyseal line.

Eliot showed by examining specimens of bone microscopically that the formation which appeared as the transverse line in the radiograph did not rest in the bone substance in the form of a line but in the form of a more or less complete stratum about one mm. in thickness which lies in a plane at right angles to the axis of the shaft, and exactly parallel to the surface of the end of the shaft. At the level of this stratum many of the trabeculae were enlarged or sent to neighboring trabeculae cross branches or bridges. This formation produced an irregular lattice work which extended transversely across the bone. Above and below this lattice formation the trabeculae had the usual shape, and they lay in the longitudinal axis of the bone, parallel to each other. The crowded, transversely placed, branching and bridging trabeculae produced a stratum more radiopaque than the normal longitudinal trabeculae, and the alternating bands of radiopacity and radiolucency were thus indicated on the radiograph.

An analysis of Table I shows that there were 17 cases studied which showed definite evidence of allergy. Of these patients, four showed no

demonstrable evidence of bone scorings on the radiographs of the left ankle and left wrist, although these four (cases 10, 14, 15, and 21) showed undoubted allergic manifestations. In case 4, the bone manifestations consisted of very faint bone scorings in the tibia, and none

TABLE I

ALLERGIC CASES

CASE NO.	NAME	AGE	BRONCHIAL ASTHMA	SENSITIVITY	RADIOGRAPHIC FINDINGS
1	J. P.	6 yr.		dust, rice, barley	bone scorings
2	L. C.	7 yr.		wheat	bone scorings
3	H. R.	3 yr.		egg, wheat, barley, potato	bone scorings
4	C. S.	5 yr.		ragweed, orris root, potato, cat and rabbit epithelium	faint bone scorings
5	J. S.	6 yr.	present		bone scorings
6	A. J.	7 yr.	present	eczema dust, feathers, horse dander	bone scorings
7	R. S.	6 yr.	present	dust	faint bone scorings
8	F. W.	4½ yr.	present	eggs, milk	faint bone scorings
9	B. A. M.	10½ yr.		wheat, silk, ragweed	faint bone scorings
10	S. J. M.	12½ yr.		ragweed	no bone scorings
11	M. M.	5½ yr.	present	house dust	bone scorings
14	C. S.	5½ mo.		eczema	no bone scorings
15	K. McE.	7½ mo.		eczema barley, chicken, pork	no bone scorings
17	J. B.	5½ mo.	present	feeding problem as yet untested	faint bone scorings
21	R. M.	5½ mo.		eczema	no bone scorings
12	J. B.	10 yr.	present	infective asthma	bone scorings (under treatment two years)
13	L. G.	10 yr.	present	skin tests negative	bone scorings (under treatment two years)

TABLE II

NONALLERGIC CASES

CASE NO.	NAME	AGE	MEDICAL CONDITION	RADIOGRAPHIC FINDINGS
16	C. A.	14 mo.	feeding problem	faint bone scorings
18	S. P.	16 mo.	upper respiratory infection	no bone scorings
19	R. P.	11 mo.	bronchopneumonia	bone scorings
20	R. T.	9½ mo.	feeding problem	faint bone scorings
22	N. G.	9 mo.	fermentive diarrhea	no bone scorings
23	V. LaR.	6 mo.	otitis media, pharyngitis, rhinitis	faint bone scorings
24	J. M.	4 yr.	common colds	marked bone scorings
25	J. G.	5½ yr.	colds in infancy	marked bone scorings
26	G. T.	4½ yr.	pneumonia at one and three years of age	faint bone scorings
27	B. A. W.	6 yr.	pertussis with good recovery	bone scorings
28	J. H.	2½ yr.	normal health	marked bone scorings
29	D. K.	4 yr.	otitis media, pertussis	marked bone scorings
30	J. K.	5 yr.	otitis media	bone scorings
31	Miss H. H.	32 yr.	nonallergic adult	bone scorings
32	Miss G. V.	27 yr.	nonallergic adult	marked bone scorings
33	Mrs. D. F.	37 yr.	nonallergic adult	bone scorings

in the radius and ulna, yet clinically, the allergic symptoms were marked, demonstrating that the bone findings did not keep pace with the clinical manifestations. Two of these allergic patients (cases 12 and 13) had been under treatment for a period of over two years, and yet they both showed definite bone scorings when examined radiographically, in spite of the fact that neither of them had evidenced any signs of allergic attacks during that period.

Fig. 5.—Wrist of young gorilla showing bone scorings in radius.

In Table II there are listed 13 cases, six of which were infants who had not walked and who were feeding problems. Of these six, two showed no bone scorings, and four showed scorings of varying degree, yet there was no sign of allergy in any of them. The remaining seven children in the nonallergic classification made up our control group, and bone scorings of varying degree were found in every one of them. Even when scorings in bone occurred they did not always disappear

as the bones grew to maturity as demonstrated in the roentgenograms of three nonallergic patients aged thirty-two, twenty-seven and thirty-seven years, respectively.

There is no evidence at the present time to show that animals suffer from allergic diseases, nor has it been possible to produce in monkeys any form of clinical allergy. For this reason we present roentgen studies on three gorillas, all inmates of the Zoological Park of New York City. Although the radiographs of these animals show evidence of rachitic bone changes, there are also transverse lines above the epiphyseal line in the shafts of the long bones studied (Fig. 5), which we believe are representative of bone scorings, and identical with those seen in the group of children studied.

A review of the literature gives evidence to the effect that transverse markings in bone, appearing proximally to the epiphyseal line on the radiographs of bones of growing children are due either to periods of variation in growth, or are secondary to starvation, dehydration, acute infectious, or deficiency disease. Other dense transverse lines occurring in the same location are produced following the introduction of yellow phosphorus, lead, or bismuth into the body during the period of bone growth.

Our experience has shown that the so-called "bone scorings" described by Todd occurred in the bones of a high percentage of children whether they suffered from allergic disturbances or not. Furthermore, they apparently did not occur in all children who suffer from allergic disturbances. With these findings before us, we feel justified in drawing the conclusion that it is hazardous to diagnose the allergic state on the evidence presented by these "bone scorings."

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CALCULATING POLLEN CONCENTRATION OF THE AIR*

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THE value of atmospheric pollen surveys in the management of seasonal hay fever and asthma is widely appreciated. In the past two decades, surveys of most sections of the United States and of parts of Canada and Mexico have been reported. In addition, many physicians find it worth-while to make daily records of the pollen content of the air in their immediate localities.

In general the method employed has been to count the number of pollen grains in a given area on a slide which has been exposed to the air for a given period. From the number counted the concentration of pollen in the air for that period has been computed. Details of this method were presented first by Scheppegrell[23, 24] whose work served as a basis for a number of subsequent modifications.

Unfortunately there was an error in Scheppegrell's calculations from his original formula. This, when magnified by the subsequent modifications of his method, makes it impossible to accept the results, as published, as true comparisons of the actual concentration of atmospheric pollen in the areas studied.

The purpose of this paper is threefold: First, to point out and to correct errors in Scheppegrell's calculations for computing the number of pollen grains in one cubic yard of air from the number caught on one square centimeter; second, to review the various methods now in use for expressing results of pollen surveys; and third, to show the necessity for and to suggest a standard accurate form to be used by workers in this field.

TO POINT OUT AND CORRECT THE ERRORS IN SCHEPPEGRELL'S METHOD

Scheppegrell[23, 24] states: "The number of pollen dropping on a given surface e.g. a plate, depends only on the number of pollen per unit of air, and the velocity of fall of the pollen grains.

"If the pollen falls with a velocity v feet per second, and there are in the air n per cubic yard, the total number N falling on a square centimeter in t hours is given by the formula

$$N = 0.143 \times n \times v \times t$$

$$n = \frac{7 \times N''}{v \times t}$$

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The constant 0.143 or $\frac{1}{7}$ is obtained as follows: If a grain falls v feet per second, it will fall 3600 v feet per hour or 1200 v yards per hour. One square centimeter equals 0.0001196 square yards, then

$$N = 1200\ v \times 0.0001196 \times n \times t$$
$$N = 0.143 \times v \times n \times t$$
$$n = \frac{7 \times N}{v \times t} = \text{number of grains per cubic yard.}$$

Having derived the above formula, Scheppegrell then calculated the velocity of fall for pollen grains of various sizes from Stokes's law. He says:

"If the particles have the form of smooth spheres of a diameter not less than 0.001 mm., it has been shown both from theory and by actual experiment that the velocity with which such spheres fall, is given by the formula:

$$v = \frac{2gr^2}{9k} \text{ (Stokes's law)}$$

where v equals the velocity in centimeters per second, g equals 980 cm., the acceleration of gravity; r equals the radius of the sphere; and k equals the coefficient of viscosity (which) for air equals 0.00018.

"By substituting the different values for the radius of the spheres and the known constants in the above formula, the velocity of pollen grains of any size can be calculated. The calculation gives exact values for the smooth pollen grains only. The values will be considerably higher in the case of the pollen with spicules, the velocity being considerably less than the calculated value."

In using Stokes's law, Scheppegrell has assumed the density of pollen to be approximately one and, therefore, omitted the density factors entirely. Although the density for pollen has not been accurately determined, preliminary experiments indicate that it is close to unity. Thus, Scheppegrell's omission of the density factor is permissible. The unfortunate error is in the fact that he used the diameter squared rather than the radius squared in Stokes's formula $v = \frac{2gr^2.}{9k}$

To illustrate his formula with an example, using a grain of 20 microns, he states:

"For example, if the diameter of the grain is 0.02 mm., $v = 0.16$ feet per second."

By substituting in the formula it is clear that he has used the *diameter* (0.002 cm.) squared instead of the *radius* (0.001 cm.) squared, for by using $(0.002)^2$ in the formula

$$n = \frac{2gr^2}{9k} \text{ we get}$$

$$v = \frac{2 \times 980 \times (0.002)^2}{9 \times 0.00018} = \frac{1960 \times 0.000004}{0.00162} = 0.484 \text{ cm. per second}$$

$$\text{or } \frac{0.484}{30} = 0.16 \text{ feet per second.}$$

Whereas actually on computing the velocity of fall in feet per second for a smooth pollen grain of 20 microns in diameter from Stokes's law we have:

$$v = \frac{2gr^2}{9k} = 2 \times 980 \times (0.001)^2 = 0.115 \text{ cm per second}$$

$$\text{or } \frac{0.115}{30} = 0.04 \text{ foot per second.}$$

Scheppegrell then substituted the velocity of fall for a grain of 20 microns (0.16 feet per second), which he had incorrectly derived, in his formula

$$n = \frac{7 \times N}{0.16 \times 24} = 1.8 \text{ N.}$$

When the correct velocity of fall for smooth pollen of 20 microns diameter (0.04 feet per second) is substituted in the above formula the following is obtained:

$$n = \frac{7 \times N}{0.04 \times 24} = 7.3 \text{ N.}$$

This is obviously greatly different from Scheppegrell's formula n = 1.8N, which has been used extensively.

The following table gives for grains of various diameters the corrected values for the velocity of fall and the formula by which the number of pollen grains per cubic yard of air may be computed from the number caught on one square centimeter in twenty-four hours.

REVIEW OF METHODS OF EXPRESSING RESULTS OF POLLEN SURVEYS

Durham,[16] who has been most active in this work, describes his method as follows:

"I adopted Scheppegrell's method of expressing results in 'pollen per cubic yard of air' and counted an area on the slide which would give this figure for ragweed. This area happened to be 1.8 sq. cm. After reporting ragweed counts in several published articles and stating my results as 'the number of ragweed pollen granules per cubic yard of air,' it was difficult to change and use any other standard of counting. Therefore, when I began reporting on other pollens than ragweed, the same 1.8 sq. cm. area of surface was counted, and the results were reported as 'the number of pollens per unit area of slide surface.' Because of the simple technique of the method, it has been adopted by a number of other workers, and most of the available studies on pollen counting are reported on this basis."

Thus in all except the early ragweed surveys, no attempt was made to express actual pollen concentration in the air.

Durham's modification of Scheppegrell's method has been adopted by Hansel,[18] Detweiler and Hurst,[5] Wilmer and Cobe,[26] and Vaughan.[25]

TABLE I

Velocity of fall and formulas for computing concentration per cubic yard from the number (N) of smooth pollen per square centimeter on slides exposed for twenty-four hours

DIAMETER IN MICRONS	VELOCITY OF FALL FOOT, SECOND	FORMULAS
10	0.01	$n = 29.1$ N
12	0.014	$= 20.8$ N
14	0.02	$= 16.6$ N
16	0.026	$= 11.2$ N
18	0.03	$= 9.7$ N
20	0.04	$= 7.3$ N
22	0.049	$= 5.9$ N
24	0.058	$= 5.0$ N
26	0.068	$= 4.3$ N
28	0.079	$= 3.7$ N
30	0.09	$= 3.2$ N
32	0.10	$= 2.9$ N
34	0.11	$= 2.7$ N
36	0.13	$= 2.2$ N
38	0.15	$= 1.9$ N
40	0.16	$= 1.8$ N
42	0.18	$= 1.6$ N
44	0.20	$= 1.5$ N
46	0.21	$= 1.4$ N
48	0.23	$= 1.3$ N
50	0.25	$= 1.2$ N
60	0.36	$= 0.8$ N
70	0.47	$= 0.6$ N
80	0.64	$= 0.5$ N

Barrett and Schwartz[3] use Scheppegrell's formula but make some allowances for differences in size of the pollen forms.

Still other investigators have not attempted to calculate the number of pollen granules per cubic yard, but have expressed their results in the number of grains caught in a given time per unit area. This unit area varies from one square centimeter to one square foot. LaRush,[20] Acquarone and Gay,[1] and Patterson and Gay[21] use one square centimeter as their unit. Duke,[7] and Duke and Durham[6] and Balyeat[2] use 0.55 sq. in., while Wodehouse[27] counts all forms found on 3.5 sq. cm. Rowe[22] considers one square inch as the proper unit. Deamer and McMinn[4] think one square foot a more comprehensible unit. Koessler and Durham[19] counted "number on plates."

TO SHOW THE NECESSITY FOR AN ACCURATE STANDARD METHOD OF EXPRESSING RESULTS AND TO SUGGEST A STANDARD FORM

The necessity for a standard and accurate method for reporting results of pollen surveys was acutely illustrated by Feinberg and Steinberg.[17] In their effort to determine the pollen content per cubic yard of air necessity to produce hay fever, they were unable to correlate the results obtained in clinical tests in which they compared the reactions produced by pollen extracts with that of atmospheric pollen. Using Scheppegrell's formula (n=1.8N) they concluded that a concentration of

25 ragweed pollen grains per cubic yard was sufficient to produce symptoms. This would mean 500 pollen grains in twenty-four hours, assuming an average intake of 20 cubic yards of air per day. This conclusion is wrong for two reasons. First, the formula has been shown to be incorrect. Second, no allowance was made for the differences size and contour make on the rate of fall of pollen. To illustrate: By the formula $n = 1.8N$ a concentration of 25 per cubic yard means N (the number caught in twenty-four hours on one square centimeter) equals 14. Using the corrected formula for a smooth pollen of 16 microns (Table I) $n = 11.2N$; then $n = 11.2 \times 14 = 156.8$ grains per cubic yard. Since ragweed is spiculated it would seem conservative to add 25 per cent to this figure. This would raise the count to 196 per cubic yard instead of their calculated 25, a total of (20×196) 3920 grains per day instead of 500.

An obvious inference from the above is that an equal number of pollens of different diameters and contours on a given area does not mean equal concentrations of these pollens. For example if 10 each of three smooth pollen grains of 14, 20, and 26 microns diameter were found on a square centimeter in twenty-four hours their concentrations would differ by (Table I):

$$\begin{aligned} n &= 16.6 \times 10 = 166 \text{ per cubic yard} \\ n &= 7.3 \times 10 = 73 \text{ per cubic yard} \\ n &= 4.3 \times 10 = 43 \text{ per cubic yard} \end{aligned}$$

a difference of nearly 400 per cent.

For practical office use in comparing day to day variations in current pollens the method of counting the number of pollen which fall on a given unit area in twenty-four hours is satisfactory. For pollen surveys, in which accuracy is highly desirable, it is recommended that all pollen grains be counted on one square centimeter as the unit area, and that the formulae in Table I be used to compute concentration per cubic yard. This requires that due cognizance be taken of the differences in diameter of the various pollens found. Unfortunately data are not available by which satisfactory allowances can be made for the effect of differences in pollen contour on the velocity of fall. Scheppegrell suggests that from 10 to 50 per cent be added for spiculated pollens, depending on the length of the spines.

SUMMARY

1. Scheppegrell's table for velocities of fall in feet per second was incorrectly calculated, as a result many reports of pollen concentration per cubic yard based on his formula are much too low.

2. For scientific accuracy the actual size of each pollen grain should be considered in calculating pollen concentration of the atmosphere. Allowance should also be for the lower velocity of fall of rough and spiculated pollen.

3. Many different units are now in use for expressing results. There should be one standard for giving results of these surveys. The author recommends that the number of pollen per cubic yard computed by the gravity method from the formulas given in Table I be accepted as the standard form.

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Special Report

HYPERSENSITIVENESS TO "ASTHMA POWDERS"*

Report of a Case

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SO-CALLED "asthma powders" are widely used for symptomatic relief. They usually consist of Stramonium leaves, potassium nitrate, and one or more of the following: the leaves of *Lobelia inflata*, mullein, other Solanaceae, swamp cabbage, *cubeb*, *chamomile*, saw palmetto, Eucalyptus, thyme, and anise or fennel seed. The therapeutic effect is thought to be due chiefly to volatile nitrites released in the smoke when the powders are burned. Some of these drugs are included for their actual or supposed antispasmodic, expectorant, demulcent, antiseptic, or aromatic effects. "Asthma cigarets" are similarly compounded.

Since these substances are used by persons who are notoriously prone to become hypersensitive to organic materials which they inhale, it was surprising that no report of hypersensitiveness to the powders nor to their major constituents could be found. The potential consequences of widespread sensitization to these substances would seem to justify the following case report:

A thirty-two-year-old white multiparous wife of a farmer had had rather severe asthma for fourteen years. She had had no other important illnesses. The asthma was worse in summer but had been present in all seasons. For several years she had seldom been entirely free of wheezing longer than a few hours, but during the cold months she would usually have only four or five severe attacks. She had had mild perennial hay fever for many years.

The inhalant history showed that in hay cutting time, cutting the grass, any dust, chicken feathers, the odor of fresh paint, certain face powders, cats, rabbit fur, cosmos, Pyrethrum sprays, grease smoke, and perhaps wool and ragweed produced asthma. She had usually had severe attacks while canning tomatoes in September. The food history indicated that buttermilk, cabbage, pork, egg, and Irish potato markedly aggravated existing mild attacks of asthma; milk caused urticaria; egg and Irish potato induced indigestion; and banana and rabbit caused edema of the buccal mucosa. The drug history was positive in that aspirin produced severe asthma.

The history of nonspecific and physical influences showed that constipation, fatigue, excitement, menstruation, cold air, and getting overheated made the asthma worse. She was practically well in the last half of 2 pregnancies.

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Routine physical, blood, urine, and stool examinations showed nothing of interest except the asthma. The only demonstrable focus of infection was a recurrent purulent postnasal discharge.

Skin tests in June, 1936, showed reactions of various strengths to some 30 allergens including inhalants, foods, and bacterial extracts.

A desensitization program, with extracts of inhalants which she could not avoid, plus avoidance of the foods mentioned in the history and those giving positive skin tests, afforded her some relief during the summer, fall, and winter of 1936 and 1937. Her adrenalin requirement was reduced to 2 or 3 small doses a week instead of a previous average of 2 or 3 doses a day. However, she continued inhaling smoke from a widely used asthma powder several times daily to relieve a slight tightness in her chest. She had used about 3 cans a month for six years. She had gotten excellent relief from it until about one year ago. Since then she had noticed that relief was obtained only for a few minutes, after which there seemed to be some aggravation of the tightness.

On February 20, 1937, while getting out of her car she spilled some of the powder on her coat and, on brushing it off, began to sneeze and in a few seconds had a violent attack of asthma which repeated injections of adrenalin relieved only partly. Morphine was required several times in the ensuing six days. She had never failed, previously, to get satisfactory temporary relief from two 5 minim doses of adrenalin.

In the clinic ten days later she was tested intradermally with a simple buffered saline extract of the powder. In three minutes there was a large wheal about 4 cm. × 6 cm. with a zone of erythema reaching almost from elbow to shoulder and around the arm. In another minute she began to wheeze violently and soon became cyanotic and almost apneic. With this reaction there was generalized urticaria. Adrenalin was injected in several places in the wheal, a tourniquet was applied above the wheal, and three 3 minim doses of adrenalin were given at once in the other arm. The reaction became less alarming in three or four minutes and was over almost entirely in about twenty minutes.

The formula of the powder as stated on the can showed it to contain Stramonium, swamp cabbage, *Lobelia inflata*, and potassium nitrate. Samples of each of these materials were obtained on the open market, and subsequent scratch tests with these showed a three-plus reaction to swamp cabbage, two-plus to Stramonium leaves, and one-plus to *Lobelia*. Reactions to intradermal tests with 1:1000 dilutions of the supernatant from thick emulsions of these materials in a buffered saline solution were four-plus to swamp cabbage, three-plus to Stramonium leaves, and one-plus to *Lobelia*. *Lobelia* in 1:10 dilution gave a two-plus reaction. Potassium nitrate, the other constituent, in 1:1000 dilution did not cause a reaction.

Passive transfer tests showed a huge four-plus reaction to swamp cabbage (1:1000) with a large zone of erythema about 6 cm. × 10 cm., and an area of subcutaneous induration about 4 cm. × 6 cm. which lasted about eight hours. There was an average four-plus reaction to Stramonium (1:1000) and a two-plus to *Lobelia* (1:1000). The control tests were all negative.

Since avoiding the asthma powder the patient reports that she quickly became better than she had been for many years. There has been no asthma nor even mild wheezing nor cough for more than five months. There has been no trace of the perennial hay fever. She has gained about 15 pounds.

SUMMARY AND CONCLUSIONS

An instance is reported of extreme hypersensitiveness to a powder containing Stramonium leaves, swamp cabbage, *Lobelia*, and potassium nitrate, such as is commonly burned for relief of asthma. Positive

scratch, intradermal, and passive transfer reactions were obtained with all three of the organic constituents. When tested intradermally with an extract of the whole powder mild anaphylactic shock resulted.

No reference to a similar report has been found. It is highly improbable that this sensitization would have been suspected had the patient not reacted so acutely to the spilled powder.

In spite of temporary relief afforded by inhalation of the nitrite fumes from such powders or cigarets, it is probable that many users are being made worse, specifically, by them. It is recommended, therefore, that patients be tested with extracts of asthma powders or cigarets before they are permitted to use them. It is further recommended that users of them be tested periodically to see if sensitization has supervened.

Annual Review

ALLERGIC DISEASES IN CHILDHOOD*

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THE previous reviewer[1] of allergic diseases in childhood for this journal, Dr. Francis Scott Smyth, in summarizing his impressions regarding the tendencies of the current literature,[2] felt that the crying need was for more fundamental studies rather than for additional clinical reports, and that detailed and careful work done with individuals or small groups promised to be of more value than statistical methods applied to large groups. These remarks continue to apply to the field of allergy in childhood.

A variety of therapeutic procedures for asthma have been discussed in the recent pediatric literature. Cohn,[3] with the majority of those who have investigated the subject, concludes from a review of the literature and his five additional cases carefully studied, that the urinary proteose described by Barber and Oriel[4] is neither specific in nature nor particularly useful in the therapy of asthma. Libman and Bigland[5] came to a similar conclusion working with adults. From the evidence at hand it does not appear that further investigation of this substance from the allergic standpoint will be fruitful. Van Loon[6] emphasizes the desirability of bronchoscopy for certain asthmatic patients to remove mucous plugs and to obtain material for autogenous vaccine. Organisms directly obtained frequently differed from those found in sputum and nasal smear cultures, which seems an important advantage in preparing autogenous vaccines. A factor not often mentioned in discussing the pathologic physiology of asthma is the lack of rigidity of the bronchial walls and consequent narrowing of the bronchial lumen on expiration, which this author observed almost constantly. Nothing indicative of bronchospasm was seen in any case. Chobot,[7] in a case report, describes a child with asthma in whom bronchoscopy disclosed bronchiectatic cavities in spite of negative roentgenograms. Improvement followed repeated bronchoscopic aspiration of the cavities. Naef's[8] report of 16 cases of asthma in children treated with stock vaccines loses significance because of the number of procedures such as environmental control, ferrous iodide by mouth, etc., which he carried out at the same time. This criticism applies to many reports on therapeutic measures in any field, but seems especially true of articles on therapy of allergic conditions. A more un-

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usual type of therapy is advocated by Lavergne,[9] who reports improvement in 20 out of 36 infants with asthma by the use of Chinese acupuncture. Protocols are not given and one questions the duration of improvement with this form of counterirritation.

Two reports deal with a search for a fundamental acid-base disturbance in the allergic individual reflecting itself in the blood or skin. Tatafiore,[10] in a small group of breast-fed infants, finds a lower than normal plasma carbonate level. Although it is not clear to the reviewer why this should be affected by injections of from 1 to 5 c.c. of maternal blood, he states that in 10 out of 12 infants where such therapy was given, the plasma carbonate level became normal and a cure was obtained. Lack of adequate protocols and statement of total duration of treatment make interpretation of his report difficult.

Nagai and Shinomiya[11] studied the pH of the subcutaneous tissue of infants with "exudative diathesis" by a method described by Nagai. Average values of 7.09 were obtained for uninvolved areas of skin. Healthy children gave average values of 7.06; young adult males, 7.11; and young adult females, 7.07. Considerably higher values were obtained in the affected areas in the exudative diathesis group, especially in cases of recent onset.

Interest in the rôle of fatty acids in eczema continues. Hansen,[12] in the most comprehensive and carefully prepared report to date, finds significant lowering of the iodine number of almost all of a group of about 30 eczema cases, and definite improvement following the administration of oils of a high iodine number. Simultaneously there was a rise in the iodine number of the serum lipids in these cases. So far as possible certain of the factors known to influence the iodine number, such as infection and previous diet, were controlled. He reports on a total of 140 infants, children, and young adults in order to afford adequate control cases both of normal individuals and other pathologic conditions. From this group additional information has been obtained. Apparently in normal individuals there is a progressive increase in the iodine number of serum lipids with age, and possibly also an increase in total lipids. One implication, of course, is that these observations may be related to the marked tendency toward improvement in infantile eczema as the infant passes into childhood. In the small group of asthma and hay fever patients Hansen studied, normal values were obtained. Bullen and Bloor[13] have also obtained normal iodine numbers in adults with hay fever and asthma. Hansen concludes that a disturbance of lipid metabolism is related at least in part to the pathogenesis of eczema. His report will doubtless prove a stimulus to further investigation of this interesting subject. Faber and Roberts,[14] and Taub and Zakon[15] had previously been unable to confirm all of Hansen's impressions. Cornbleet,[16] on the other hand, believes that maize oil produces beneficial results in adult eczema. An additional report is that of Epstein and Glick,[17] who failed to obtain

benefit from the administration of linseed oil by mouth in a group of 35 eczema cases in infants, children, and adults. In the nine cases in which it was investigated they found no consistent rise in the iodine number as a result of treatment.

Freudenberg and Schornstein[18] have also investigated blood fat in infants with eczema and seborrheic dermatitis. They too find an increase in total lipids as well as the cholesterol fraction with increase in age during infancy, but they were unable to obtain a consistent normal curve after a standard fat meal. Variations in values were too great to admit of interpretation. They employed a fat-poor and chloride-poor diet with best results in seborrheic dermatitis and the types of eczema in which a seborrheic element was present.

Signorelli,[19] in a well-presented article, reports the eczema problem from the pediatrician's point of view. Despite a voluminous literature on the subject, he finds the status of its study unsatisfactory and confusing. In the present state of our knowledge he cannot accept any single concept of etiology, and he emphasizes the multiplicity of factors known to be concerned. With the interpretation of positive skin tests not yet settled, he believes that fat metabolism is of greater importance than protein sensitivity and feels that a good general nutritional status of the patient with avoidance of under-nutrition or over-nutrition takes priority over even local treatment. He obtains decided benefit from olive oil by mouth. While no new concepts are presented, the older ones are not colored by bias along one particular line.

Brock and Röntsch[20] find that milk-free diets used in infantile eczema are frequently low in fat and sodium chloride (as is the diet employed by Freudenberg and Schornstein) and usually contain no animal protein. He obtained better weight gains in rats with foods derived from soy bean and bran than with an almond-milk preparation. The addition of sodium chloride did not give demonstrable improvement even though salt restriction had been extreme. A more practical experiment was that of Lane[21] who followed a group of children over a period of years on an exclusively vegetable diet which included a large amount of almond-lac daily (prepared from almond, peanut, soy bean, and vegetables). These children grew exceptionally well and none of them developed allergic symptoms over periods of up to seven years. This diet was also used in many cases of infantile eczema with improvement, which the author felt was due more to its general nutritional qualities than to avoidance of any specific protein factors.

Additional reports reflect the interest in blood platelets and eosinophil and total white blood cell changes associated with allergy. Squier and Madison[22] express the opinion that in addition to the numerous drugs which have been proved to cause thrombocytopenic purpura, food allergy can also be responsible, and they cite a small number of

cases in illustration. The degree of fall is apparently small and may be confined to a limited number of the offending foods in a given individual. The other offenders, while capable of producing an eosinophilia and leucopenia, fail to alter the platelet count significantly. Considering the recognized difficulty in making accurate platelet counts, and the known as well as the yet undiscovered causes of their fluctuations (Lorenz[23] ascribes a platelet regulating mechanism to vitamin A!), additional investigation will have to be done before the value of thrombocyte counts in allergic individuals is known. Squier and Madison classify allergic purpura as anaphylactoid, in which increased capillary permeability is present, and thrombocytopenic, in which lowering of the platelet count is also present. They are of the opinion that other types of allergens will probably be shown to bring about a thrombocytopenia with purpura in certain individuals, and apparently this is already proving to be the case. Three instances cited by Kugelmass[24] may illustrate this point. In three allergic children thrombocytopenia and purpura followed the last of a series of pertussis vaccine injections by ten days to three weeks. His report is open to criticism, however, since purpura had occurred 10 months prior to the first injection in one of the cases, and in another it recurred two and three months after the last injection, a rather long interval after the supposedly etiologic immunization. Furthermore, Wright and Bacal[25] report an interesting occurrence of purpura in an apparently healthy boy following a routine Mantoux tuberculin test. The reaction occurred close to the height of the tuberculin reaction which was markedly positive, and it was associated with a leucopenia and an eosinophilia of 29 per cent. The report is of interest because it grants some of the characteristics of the immediate type of allergic reaction to a reaction of the delayed type. Although no claim has been made to the reviewer's knowledge that primary purpuras in children are always based on an allergic or atopic mechanism, Bartley[26] objects to "forcing the anaphylactic key into locks it was never intended to fit." He states that in a follow-up of 12 cases of "primary purpura" in children, including the Henoch and Schönlein types as well as purpura simplex, he could find little evidence for allergy in the family or personal histories. There was considerable evidence for the rôle of infection and no recurrences after one to nine years.

While the limitations of passive transfer in food-sensitive children, as reported by Chobot and Hurwitz,[27] agree with the observation of Romanoff and Brooks[28] that pollen-sensitive serum transferred much better than lamb-sensitive serum, certain criticisms of the former authors' work are apparent. Their definition of a positive transfer reaction is based on its size, and also in some instances, on the presence of pseudopods, whereas the accepted conception of a positive reaction relates not to its dimensions but to the excess of this reaction over its particular control site. Chobot and Hurwitz do not mention

using control sites. Again they use the results of ingestion of a food twice a day for two days as evidence for or against the existence of clinical food allergy. While this would probably bring to light most instances of food allergy, it cannot be relied upon to disclose all instances of clinical food sensitization. Finally, as is true with all allergens, the failure to obtain a positive reaction in clinically sensitive individuals may at times rest on unsatisfactory testing material. On direct tests food antigens have been recognized as giving the least satisfactory result.

Pratt[29] found 80 per cent of a group of 26 children with positive tests to house dust gave positive transfer reactions. The total group they studied consisted of 71 children with perennial asthma, of whom 79 per cent gave two plus or greater reactions to house dust by scratch test. As would be expected with an inhalant allergen, the frequency and severity of the sensitization increased with the advancing years of childhood.

The consolation taken by parents of allergic children, often themselves allergic, in the statement sometimes made that superior mental traits embellish the allergic constitution,[30] is ill founded, according to Piness, Miller, and Sullivan,[31] who found no essential difference in the intelligence rating of 145 allergic children when compared with a group of unselected children in the public schools of the same city.

Ratner,[32] in a study of large groups of allergic and normal children, was unable to find a greater incidence of allergy in the families of the allergic group. He believes the development of a sensitization is due to the chance occurrence of certain factors and not to an hereditary mechanism. The reviewer feels that the evidence at hand is still greatly in favor of the hereditary theory. The analysis of family histories by Wiener, Zieve and Fries,[33] as well as the report of Spaich and Ostertag[34] on allergic disease in twins, supports such a conception. The first mentioned authors and Harley[35] have attempted to link the genes for allergic disease with certain known genes, but were unable to do so.

It is interesting to note that London[36] finds that 6.6 per cent of the patients seen by a pediatrician seek relief from a complaint of an allergic nature. This is an additional argument in favor of the plea of the Association for the Study of Allergy for more hours devoted to the teaching of allergy in medical schools.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL FEINBERG, M.D., CHICAGO

The Occurrence of Constitutional Reactions in the Treatment of Hay Fever and Asthma: Analysis of the Causative Factors. Furstenberg, F. F., and Gay, L. N.: Bull. Johns Hopkins Hosp. **60**: 412, 1937.

The authors analyze the frequency and causes of constitutional reactions among their clinic and private patients. In 43,771 therapeutic injections of allergens there occurred 87 constitutional reactions. Of those treated with pollen in private practice 11.7 per cent, or 0.16 per cent of the injections, resulted in reactions. Of the clinic cases 5.9 per cent, or 0.33 per cent of the injections, reacted. No private patient had more than two reactions while clinic patients had as many as five. The authors have never experienced an intravascular or back-seepage reaction.

Furstenberg and Gay list as the most important causes of constitutional reactions: the individual tolerance of the patient for a given dose and change from a large volume of a weaker extract to a small volume of a stronger extract. As lesser causes they list: the use of too concentrated extracts, too frequent injections, too large an increase in dose, too large an initial dose, errors in dosage, and improper technique of administration. The authors admit that they have not been able to demonstrate any evident cause for reactions in one-half of the clinic and two-thirds of the private cases.

Further Observation on Rapid Hyposensitization. Waldbott, G. L., and Ascher, M. S.: Ann. Int. Med. **10**: 1556, 1937.

Rapid hyposensitization is advocated in instances of known sensitivity when relief is desirable in a short time or when only a brief period is present for preparing the patient to withstand his causative antigen. This is particularly applicable to pollen therapy. Rapid hyposensitization, in order to be safe and effective, must consider the following principles. The initial dose must be sufficiently low so as not to produce much local swelling. The doses and intervals should be carefully gauged by the edema of the preceding injection. Adrenalin should be avoided in order not to mask the local reactions. The authors find that they frequently reach a dose of 7,000 or 8,000 pollen units in five or six days.

Hay Fever. I. The Effect of Pollen Therapy on the Skin Reactions. II. A Reaction-Inhibiting Substance in the Serum of Treated Patients. Harley, D.: J. Path. & Bact. **44**: 589, 1937.

The author records the observation that no appreciable reduction of the prick test following pollen therapy occurs until a dose exceeding 5,000 Noon units has been administered. He thinks that the failure to realize the fact that a definite dosage must be attained before reduction in skin tests occurs has been responsible for the discrepancy of reports of different authors with regard to the effect of pollen therapy on the skin reaction.

Harley confirms the work of Cooke *et al* in the demonstration of a reaction—inhibiting substance in the serum of grass-sensitive patients after treatment with grass pollen. This substance blocks the reactions of normal skin sites to serum-pollen mixtures. The block occurs between the reagin and the allergen and not between the reagin and the skin cells. This reaction-inhibiting substance apparently acts by attaching itself to the reagin, thus preventing the allergen from uniting with the reagin. The attachment of the reaction-inhibiting substance does not appear to be very stable. The skin site is found to be fully reactive to pollen extract twenty-four hours later.

Hay Fever in Alberta. Jamieson, H. C.: Canad. M. A. J. **36:** 595, 1937.

Jamieson divides Alberta into three zones. The northern zone has only spring hay fever, due principally to poplars. The central zone has both spring and midsummer hay fever, the latter principally due to June grass and timothy. The southern section has, in addition to the above, fall hay fever from Russian thistle and sage. In the southernmost section of Alberta a small amount of ragweed is found.

Hay Fever and Asthma During and After Jaundice. Boros, E.: J. A. M. A. **109.** 113, 1937.

The author cites the case history of a ragweed hay fever patient who became jaundiced following the use of cinchophen for neuritis. There was marked evidence of liver damage with a high degree of icterus and ascites. During his illness (1935) the hay fever season appeared without any evident respiratory symptoms in the patient. He recovered from his icterus and other toxic manifestations so that he was apparently well. The 1936 ragweed season arrived and during the entire season no hay fever symptoms occurred. Skin tests at that time showed a positive reaction to ragweed, although the conjunctival tests were only mildly positive. The author theorizes that the liver damage caused some change in the mechanism of allergy.

Desensitization by Oral Administration of Pollen Extracts. Stier, R. F. E., and Hollister, G.: Northwest. Med. **36:** 166, 1937.

Stier and Hollister experimented with pollen extract by mouth in the treatment of a series of hay fever patients. They claim to have obtained satisfactory results in 78 per cent by this method. The best results were obtained by coseasonal treatment. The pollens used consisted of a large variety, but apparently did not include ragweed. The doses were three to four drops of 1:100,000 extract to a maximum dose of 21 drops of 1:100. Most patients required a quantity of the 1:100 solution daily. Mild systemic symptoms occurred at times but no severe reactions were noted.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., AND JOSEPH GOODMAN, M.D., NEW YORK CITY

Quantitative Tuberculin Testing in Tuberculosis of the Skin, in Tuberculids and in Skin Diseases of Doubtful Tuberculous Origin. Bonnevie, P., and With, T. K.: Arch. Dermat. & Syph. **175:** 181, 1936.

The authors performed their studies by means of intracutaneous tests using old tuberculin in dilutions of 1:10, 1:100, 1:1000, etc., up to 1:1,000,000. The results were expressed as a "tuberculin-exponent" (pTB) which is the logarithm of the concentration at which a reaction first occurred. Thus, a patient reacting to the

1:10 dilution and showing no reaction to the more dilute tuberculin has a pTB of 1; one showing a reaction to a dilution of 1:10,000 and no reaction to more dilute tuberculin has a pTB of 4, etc.

Graduated tuberculin tests were performed on 435 patients with skin diseases not of tuberculous origin, on 294 patients with lupus vulgaris, 74 patients with other forms of tuberculosis of the skin, 76 patients with lupus erythematosus, 25 patients with sarcoid of Boeck, 7 patients with granuloma annulare, 93 patients with pulmonary tuberculosis, and 198 patients with glandular tuberculosis.

The tuberculids as a group showed the greatest sensitivity to tuberculin (pTB greater than 4). The group with lupus showed a definite hypersensitivity, the average being a little below that of the tuberculid group. Patients with lupus vulgaris who were found to have a pTB of 0, 1, or 2, were for the most part found to have pulmonary tuberculosis as well as tuberculosis of the skin. With active pulmonary tuberculosis the pTB was most often found to be 2 or 3. However, glandular tuberculosis was found to show approximately the same level of hypersensitivity as lupus vulgaris.

The level of tuberculin sensitivity in the group with lupus erythematosus was found to be slightly higher than that of the normal group. This fact as well as other studies of these patients led the authors to suggest that lupus erythematosus develops on a "tuberculous terrain," that the disease in itself does not increase the tuberculin sensitivity, and that in the absence of tuberculin sensitivity the diagnosis of lupus erythematosus must be made with great care.

Of the 25 cases of sarcoid of Boeck, none showed a pTB greater than 2. The tuberculin sensitivity was thus definitely less than that found in the normal control group.

For a wealth of detail the original of this excellent study should be consulted.

Study on the Allergic Metabolism Reaction in Isolated Tissues With Special Reference to Allergic Skin Affections. Boström, G.: Acta dermat.-venereol. **18**: Supp. 4, 1937.

Using the Warburg respiration chamber, the author (in conjunction with others, including Hellerström (Delib. Cong. Dermat. Internat. 9, **1**: 229, Budapest, 1935.) and Schaumann (Acta dermat.-venereol. **18**: 90, 1937.) has studied the respiration and anerobic glycolysis of tissues from normal and allergic animals and humans. The addition of sera and purified proteins had no significant effect on the metabolism of isolated slices of skin, kidney, liver, etc. However, the addition to the isolated tissue of a protein or serum to which the animal was sensitized produced a characteristic metabolic change; large doses stopped or decreased metabolism, smaller doses gave only an increase, and still smaller doses had no effect whatsoever. Guinea pigs, rabbits, and mice which were sensitized by repeated injections of antigen in one skin area showed the characteristic metabolism reaction in the internal organs and in the skin distant from the site of injections. Not until two weeks had elapsed after completion of the sensitizing injections did the isolated skin of the injected area show the specific response to the addition of antigen. Passively sensitized animals also showed this metabolic change twenty-four to forty-eight hours after the injection of serum from actively sensitized animals. A study of sensitized animals by the usual methods (anaphylactic shock, Schultz-Dale experiment, passive transference experiment, and precipitin reaction) showed that the results of the metabolism reaction were in close agreement with the results of the older methods. The isolated tissue also showed a desensitization phenomenon comparable to that encountered in the Schultz-Dale experiment.

The addition of histamine to the isolated tissues of the normal guinea pig (only one animal used in this experiment) inhibited glycolysis when the concentration was

high (for example, 1:1000) but had no effect when the concentration was low (for example, 1:1,000,000). The addition of histamine to the sensitized tissue did not inhibit the subsequent production by the addition of the specific antigen of the typical metabolism reaction (again only one animal used in this experiment).

Tests by this technique of isolated slices of human skin revealed that in erythema induratum the whole skin shows the characteristic metabolism reaction to tuberculin, while in erythema nodosum of tuberculous origin only the skin from the affected areas reacted, the normal skin showing either a weak reaction or none at all. The skin from cases of sarcoid of Boeck sometimes showed a reaction like the skin from patients with erythema induratum (2 cases), sometimes a negative reaction (3 cases), and sometimes a peculiar delayed reaction (4 cases). The results of the metabolism reaction in these diseases corresponded closely with the results of the tuberculin test.

In various forms of syphilis a comparison of the *in vivo* and *in vitro* luetin test showed good agreement between the two, except that in secondary syphilis the metabolism reaction was strongly positive while the skin test *in vivo* was either weakly positive or negative. Studies by this technique of a few cases of lymphopathia venerea, fungus infections, urticaria, atopic dermatitis, drug eruptions, and contact dermatitis are also reported. For details of these interesting experiments the original must be consulted. Except in the instances of tuberculosis and syphilis the number of cases studied is not large enough to permit the drawing of definite conclusions.

The skin used in the metabolism test, removed from the subject by means of a Thiersch knife, consists almost entirely of epidermis, but small bits of cutis from the tops of the papillary bodies adhere to it. The author believes that his experiments do not prove which tissue (epithelium or cutis) is the site in which the reaction is released. However, it is quite certain that the metabolism reaction takes place principally in the epithelium. These experiments furnish evidence that epithelium and cutis form a "functional unit" in allergic reactions.

Most important is the fact that the metabolism reaction offers for the first time a quantitative *in vitro* procedure for the study of allergic diseases.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

Active Sensitization of White Mice. Burdon, K. L.: Proc. Soc. Exper. Biol. & Med. **36**: 340, 1937.

The author studied the production of active anaphylaxis in white mice. He found that repeated sensitizing injections increased the degree of anaphylactic sensitivity. Sensitization was produced equally well with horse serum and egg white by the intravenous or the intraperitoneal route. It was demonstrated as early as the ninth day and persisted for at least forty days. The highest percentage of anaphylactic deaths occurred among those mice sensitized by four intraperitoneal injections at five day intervals, and shocked by the intravenous route.

Treatment of Serum Serving to Remove Its Serum Sickness-Causing Activity. Jones, L. R., and Fleisher, M. S.: Proc. Soc. Exper. Biol. & Med. **32**: 621, 1937.

In previous communications, the authors reported a reaction appearing on the ears of rabbits subsequent to the injection of whole horse serum or fractions thereof, which they considered analogous to serum sickness in human beings. More

recent studies by the same authors suggested that the substances causing serum sickness might be agents other than the proteins themselves, although they appeared to be associated with the pseudoglobulin fraction of the serum.

The writers now report that by adding adequate quantities of alkali or acid to normal or immune serum, heating, and then neutralizing the mixture, the factor responsible for serum sickness can be destroyed. Rabbits receiving serum treated in the above manner do not develop serum sickness, while 60 per cent of the animals injected with untreated serum manifest symptoms. From 50 to 100 per cent of their original protective properties were retained by the treated sera.

Tuberculin Allergy Produced by Parenteral BCG Vaccination. Kereszturi, C., Rosenberg, H. A., and Park, W. H.: Am. Rev. Tuberc. **36**: 90, 1937.

The authors report on the development of allergy to old tuberculin following parenteral BCG vaccination based upon the study of 41 children vaccinated subcutaneously and 292 vaccinated intracutaneously. All tests were done by the Mantoux method of intracutaneous injection of 0.1 and 0.2 mg. of old tuberculin. The minimum reaction considered positive was one in which the induration measured at least 10 mm. in diameter. Smaller doses of vaccine were used for subcutaneous injection than for intracutaneous injection in order to reduce the number of cold abscesses at the site of inoculation.

The authors found that allergy develops more frequently and more rapidly in the intracutaneous group than in the subcutaneous group. The highest incidence of allergy in both groups occurred at the end of the sixth month. The optimum dose for the production of allergy with the intracutaneous technique was 0.15 mg. The incidence of the development of allergy was not influenced either by the age of the patient or by the age of the vaccine (1 to 10 days). Among those cases exposed to open tuberculosis either before or after vaccination, a greater number of positive Mantoux tests developed than among those vaccinated cases not so exposed. The writers found some children who could not be made allergic despite several vaccinations with BCG.

Analyses of Composite Antigens by the Schultz-Dale Technic; Further Experimental Analyses of Trichophytins. Judassohn, W., Schaaf, F., and Wohler, G.: J. Immunol. **32**: 203, 1937.

In earlier studies the antigenic content of different trichophytins was analyzed by means of the Schultz-Dale technic. Desiccated purified preparations of *Achorion quinckeanum, Trichophyton gypseum* and *Achorion schoenleinii* were used. The authors demonstrated that the trichophytin employed contained several antigens: one derived from the culture medium (N-antigen), another common to all three trichophytins (H-antigen), specific antigens present in each of the trichophytins, and an antigen common to *Achorion quinckeanum* and *Trichophyton gypseum* but lacking in *Achorion schoenleinii.*

In the present communication the authors, using the same technic, have repeated and elaborated on these earlier experiments, using the same trichophytin preparations and an additional one prepared from Epidermophyton Kaufman-Wolf.

Confirming their earlier findings, the writers show that trichophytins represent antigenic mixtures. Antigens characteristic for each individual fungus and others common to certain groups of different hyphomycetes were demonstrated. Common antigens were found in hyphomycetes and oidiomycetes. The authors have set up provisional antigenic formulas for the trichophytins studied and on the basis of these propose an immunologic classification of the fungi.

The article is introduced by a comprehensive analysis of the authors' earlier studies by M. Sulzberger.

The Effect of Experimental Acidosis on the Production of Immune Bodies in the Rabbit. Brandes, W. W., and Cairns, A. B.: J. Immunol. **32**: 137, 1937.

The authors report the results of experiments performed to ascertain whether precipitin and agglutinin production in the rabbit are affected by acidosis.

The production of agglutinins for typhoid bacilli, of precipitins for ovalbumin, and the simultaneous production of both antibodies in the same animal were studied in normal and acidotic rabbits. Acidosis was induced by daily intravenous injections of from 1.0 to 2.5 c.c. of a 12 per cent ammonium chloride solution.

The authors demonstrated that rabbits with acidosis developed agglutinins and precipitins in much lower titers than normal animals. This effect of acidosis was noted in animals injected with each or both of the antigens.

The similar behavior of the agglutinins and precipitins in this experiment is in accord with the unitarian theory of antibodies, but is by no means conclusive proof of the same.

Effect of Immunization on the Distribution of Serum Proteins. Lin, S. C., Chow, B. F., and Lee, K. H.: Chinese J. Physiol. **11**: 201, 1937.

The authors present a quantitative study of the relationship between the antibody content and the distribution of the serum proteins. Sera from rabbits and horses immunized against pneumococcus Type I were used. The antibody content was determined by the quantitative agglutination method of Heidelberger and Kabat. Fractionation of the serum with methyl alcohol of different concentrations at a low temperature was found to be a convenient method for studying the complete distribution curve of serum proteins.

The writers note that after immunization the amount of euglobulin in rabbit serum precipitable by 10 per cent methyl alcohol did not show any significant change, while the amount of total globulin precipitable by 35 per cent methyl alcohol increased to about three times the original value. In the case of horse serum, the increase of total globulin was mainly due to the increase in euglobulin. These findings agree with the authors' previous reports that in rabbit serum the Type I pneumococcus antibody lies mainly in the pseudoglobulin fraction, while in horse serum, it is mainly in the euglobulin.

In rabbit immunizations, it was noted that the rapid increase in globulin ran almost parallel with the increase in antibody content. After the discontinuation of immunization, both the antibody content and the serum globulin decreased very rapidly. With horse serum the increases were less rapid.

Otolaryngology

UNDER THE DIRECTION OF FRENCH HANSEL, M.D., ST. LOUIS

Clinical Problem of Allergy in Relation to Conjunctivitis and Iritis. Woods, A. C.: Arch. Ophth. **17**: 1, 1937.

Woods gives an excellent summary of the present status of the relationship between allergy, iritis, and conjunctivitis. He describes three types of allergic conjunctivitis: first the acute edematous type, characterized by sudden onset, edema, conjunctival congestion, and lacrimation. This type is most commonly seen with asthma and hay fever. The second type is the so-called edematous eczematous type, characterized by eczema of the lids and neighboring skin, edema of the lids, profuse lacrimation, conjunctival congestion, and slight chemosis. This type is caused by drugs, such as butyn, atropine, etc., and is always accompanied by marked hyper-

sensitiveness of the skin as shown by positive patch tests with the offending substances. The third type is the chronic recurrent irritative conjunctivitis, often associated with low grade folliculosis with sharp exacerbations and normal bacteriologic findings. Pollens, epidermals, foods, etc., may be the cause, and the conjunctivitis may be the only manifestation of allergy in the individual. Woods discusses at some length the relation of staphylococcus toxoid to conjunctivitis.

Woods reviews our present understanding of the nature of vernal catarrh and enumerates the reasons for classifying it as an allergic disease. He states that certain types of recurrent uveitis and iritis are allergic reactions, resulting from sensitization and intoxication of the tissues by bacterial products. He further states that there is little justification for the use of vaccine therapy in the treatment of recurrent iritis because of the difficulty in determining the causative organism.

Retinal Allergy—Report of a Case. Plumer, J. S.: Arch. Ophth. **17**: 516, 1937.

Plumer reports a case of retinal allergy. The patient was a physician, aged thirty-five, who complained of blurring of vision of the left eye, of sudden onset, and of two weeks' duration. There was a reduction of visual acuity, blurring of vision of the left eye, and a slight congestion and haziness of the left macula. Removal of the tonsils and infected teeth resulted in the condition's clearing up. A few weeks later, however, there was a recurrence of symptoms. At the onset the patient had ingested peanuts. There was a personal history of migraine, hay fever, and intolerance to chicken meat. Positive skin tests were obtained to chicken meat, early grass pollens, beans, cottonseed, and peanuts. Removal of these substances from the diet resulted in the clearing up of the symptoms.

Paustereorama of Polypous Mucous Membrane of the Sinuses. Mittermaier, R.: Hals-, Nasen- u. Ohrenarzt, Teil I **27**: 2, 1936.

Mittermaier has suggested the use of a new contrast medium for x-ray examination of the sinuses which is especially useful in cases in which there are polypoid changes in the mucous membrane. The contrast medium used consists of barium sulphate to which tragacanth has been added. This medium is found most suitable because of its tendency to adhere to the mucous membrane. It was found to outline the contour of the mucous membrane and yet leave the cavity of the sinus free so that an air space remains.

Use of the Benzedrine Inhaler for Children. Vollmer, E. S.: Arch. Otolaryng. **26**: 91, 1937.

Vollmer has made an investigation of the use of the benzedrine inhaler in acute colds, sinusitis, and allergy in children. The idea of the investigation was to determine the feasibility of administering benzedrine to children by dry inhalation, the therapeutic effect of such inhalation, and the possible occurrence of toxic effects. It was used in 75 cases of acute rhinopharyngitis and sinusitis with relief of the obstructive symptoms. In asthma, the nasal obstructive symptoms were definitely relieved. No untoward symptoms were noted from the use of the inhaler.

Arthus' Phenomenon in Oropharyngeal Mucosa. Arslan, K.: Arch. ital. di otol. **48**: 18, 1936.

Arslan was able to produce the Arthus' phenomenon in the *velum pendulum palati* of rabbits by means of a submucous velar injection of horse serum repeated at regular intervals. The development of the Arthus' phenomenon was found to be slower in the oropharyngeal than in the submucous tissues of rabbits, and the

oropharyngeal lesion is smaller than the subcutaneous lesion—probably because the reactivity of the submucous tissue to local sensitization is diminished as compared to that of the subcutaneous tissue. The same experiments carried on in guinea pigs failed to produce the Arthus' phenomenon in the oral mucosa.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

The Vaccine Treatment of Asthma in Childhood. Naef, E.: New Orleans M. & S. J. **89:** 404, 1937.

In 16 unselected cases of asthma in children, stock pertussis or *Micrococcus catarrhalis* vaccines were administered intramuscularly one to three times a week for five weeks. No skin tests of any kind were done as their use had proved unsatisfactory in the author's opinion. However, in addition to the vaccine, offending proteins as disclosed by history were eliminated and a "low histidine diet," calcium gluconate and ferrous iodide were prescribed routinely. On this regime 11 of the 16 cases were considered cured, three improved, and two were unimproved.

The Composition of an Average Pediatric Practice. London, A. H.: J. Pediat. **10:** 762, 1937.

The author found that of the first 1,500 children under his care in private practice in Durham, North Carolina, 6.6 per cent had reported at some time with a complaint of an allergic nature. Forty-five, or 3 per cent, of the entire group consulted him because of eczema; 35, or 2 per cent, because of asthma; and the other 19 complained of urticaria, hay fever, abdominal allergy or dermographia in the order given. The high incidence of asthma is in accord with the observations of other physicians in the community. Contamination of the air with tobacco dust had been suspected as a cause, though very few of the patients showed a skin reaction when tested with tobacco. Skin tests as a guide in treatment of the eczema cases were disappointing. Tar preparations cleared up most of the mild eczemas, and the author was fortunate in that all of the eczemas eventually cleared up with the passage of time.

Urinary Proteose. Cohn, J.: M. Rec. **145:** 8, 1937.

A review of the literature on urinary proteose in relation to allergy is given, and in addition the author reports on its lack of specificity on skin testing and lack of value in treatment in five asthmatic children. He was unable to obtain positive reactions using strengths up to 1 to 100 either directly on the patients or by passive transfer. Treatment with autogenous proteose in these five patients was without benefit or aggravation.

Allergic Exanthemata of the Newborn. Mayerhofer, E.: Arch. f. Kinderh. **111:** 51, 1937.

Mayerhofer states that the report of Wolff (ibid. **109:** 89, 1936) of a two-day-old child with urticaria is not very unusual. In his opinion it fits the group of allergic rashes of the newborn which he first described and which is recognizable in about half of all newborns, usually as a papular erythema occurring within the first four days. It is the same condition as Leiner's "toxic newborn exanthem."

Unsaturated Fatty Acids in Eczema. Epstein, N. N., and Glick, D.: Arch. Dermat. & Syph. 35: 427, 1937.

Among a group of dermatologic patients studied by Epstein and Glick were 35 instances of eczema in infants, children, and adults. No improvement was obtained from administration of practicable amounts of linseed oil by mouth (¼ to 2 oz. daily) with the exception of one child in whom improvement occurred, but could not definitely be attributed to the oil. Two children exhibited flare-ups on one occasion during the period of treatment with oil. In the nine cases where it was investigated there was no consistent rise in the iodine number of the serum fatty acids as a result of treatment.

Eczema From the Pediatrician's Standpoint. Signorelli, J.: J. M. A. Alabama 6: 197, 1936.

The unsatisfactory status of the study of eczema in spite of the voluminous literature is emphasized. The author feels that there is no one etiologic factor which can be considered the primary cause of eczema. He points out the interpretation of positive tests is apt to be especially difficult. The delicate, easily irritated nature of the infant's skin, the structure of which is quite different from that of the adult, is but one factor. While specific protein reactions may play a part, he feels that fat metabolism is of greater importance, and that the general nutritional status of the patient, with avoidance of undernutrition and overnutrition as well as poorly balanced diets, must receive proper attention before local treatment can be successful. He combines these principles with the administration of olive oil by mouth, while protecting the skin from external irritants. He believes that eczema presents a special pediatric problem requiring the cooperation of the pediatrician with the allergist or dermatologist before success can be expected.

Miscellaneous

Hormone Sensitization Test for Pregnancy. Greene, G. B.: South. M. J. 30: 727, 1937.

The test first described by Porges and Pollatscheik in 1929 has been reviewed from time to time. It is based upon the theory that in a pregnant woman, the anterior pituitary-like substance thrown into the blood stream would find her not sensitive to this substance, since she has become accustomed to it, whereas, the nonpregnant woman, having none in her circulating blood, would react to its intradermal injection.

The test consists in the injection of two minims of "Antuitrin S" intradermally. A positive reaction consists of a wheal and zone of erythema within half an hour or less.

A group of patients with various conditions other than pregnancy were examined —menopause, menstruation, and normal nonpregnant individuals. In all these patients the test was positive. In twelve postpartum and in twenty pregnant women the test was negative.

The author recognizes that the number of tests is limited, but the perfect accord between the negative test and pregnancy in all cases, and the positive findings in all others, warrants its further trial.

Generallergy and Metrallergy. Goodall, J. R., and Power, R. M. H.: Am. J. Obst. & Gynec. 33: 194, 1937.

The authors coined the names in the title of their article. They derived them from Greek words to denote allergy of the genital system and of the uterus in particular. They state that all authorities on allergy emphasize that no system is immune from its influence. They examined the genital system in regard to dysfunction and found that allergy manifests itself in the pelvic system in the following forms: general pelvic edema and free fluid in the pelvic cavity, chronic endometrial edema and hyperplasia, acute endometrial edema associated with phases of the menstrual cycle, menorrhagia, acute menorrhagia, metrorrhagia, dysmenorrhea, leucorrhea, and vaginitis and vulvitis.

Case reports are given to illustrate that some of the above disturbances may be allergic. The authors believe that hypothyroidism is an expression of allergy, likewise the absence of free hydrochloric acid, for complete relief was attained in some of these exemplary cases by the use of thyroid and acid alone. In other cases, there is an allergic background but no specific allergen was discovered to account for symptoms. In one patient the ingestion of bread caused the following presumably allergic symptoms: chilliness, cold extremities, cold perspiration, acceleration of the heart beat, precordial pain and epistaxis. The authors believe that many conditions not generally attributed to allergy are allergic basically. These include neurasthenia, acidosis, and a variety of others.

Discussion of this paper was unfavorable.

The Therapy of Anaphylactic Conditions With Large Amounts of Calcium. Undritz, E.: Deutsche med. Wchnschr. 63: 98, 1937.

The author cites two cases with severe anaphylactic symptoms, one following an injection of tetanus antitoxin intragluteally, and the other following what appeared to be an insect bite. Calcium injections given intravenously and intramuscularly in large doses temporarily checked these reactions; and on their return, the same calcium therapy again held them in check. The process was repeated as often as symptoms returned until the patient recovered.

A proprietary calcium solution was employed for intravenous use, the initial dose being 10 c.c. of a 10 per cent solution intramuscularly, and 10 c.c. of a 20 per cent solution intravenously (3 gm. calcium salt in all). The author stresses the use of large doses promptly.

Autogenous Urinary Proteose in Asthma and Other Allergic Conditions. Libman, J., and Bigland, A. D.: Brit. M. J. 1: 62, 1937.

The authors reviewed the work done to date on the relation of urinary proteose to allergic manifestations, and carefully studied a series of patients whom they treated with autogenous proteose. They have been led to believe, together with others, that the zone of erythema obtained at the side of intradermal injection of urinary proteose is probably nothing more than a local toxic reaction and is not in any way specific.

The therapeutic benefit obtained with injections of autogenous urinary proteose in cases of asthma was about the same as that obtained with peptone. Any specificity which may be claimed for the former method does not outweigh the many advantages of a simpler and more general form of desensitization such as can be obtained with peptone.

The therapeutic results obtained in cases of urticaria were encouraging and of sufficient interest to warrant further investigation.

Book Review

CLINICAL ALLERGY—MANIFESTATIONS, DIAGNOSIS AND TREATMENT. BY ALBERT H. ROWE, 1937, pp. 812, Lea & Febiger, Philadelphia.

The development of allergy in its many aspects is moving at a pace with which few can keep up. Consequently, a new book which assembles data on any phase of the subject and brings it up to date is a welcome asset. Rowe has done this, and the material is all there.

To an allergist it is a valuable reference book, well indexed, containing 80 pages of bibliography including recent publications, alphabetically arranged, and meticulously conventional in its form.

To one not versed in allergy and who needs guidance, the book represents an individual point of view to a large extent. Great emphasis is placed on food allergy, so much so, that of the two chapters of about equal length dealing with the fundamental aspects of the subject, one is devoted entirely to food allergy. Again, in presenting clinical manifestations, gastro-intestinal allergy comes first. The uninformed will find other examples wherein emphasis, or the lack of it, may thus lead him. There is no chapter on hay fever the subject of which is included under "Bronchial Asthma," since pollinosis is a common cause of asthma. This chapter contains 121 pages. "Allergic Toxemia," on the other hand, has a chapter to itself, of but three pages. Many topics which have been thought by some to be related to allergy are dealt with impartially. They include various urogenital disorders, cardiovascular disturbances, fever, periarteritis nodosa, and various others. These are all supported by relevant literature.

The book is well written and is a valuable addition to the growing library devoted to allergy.

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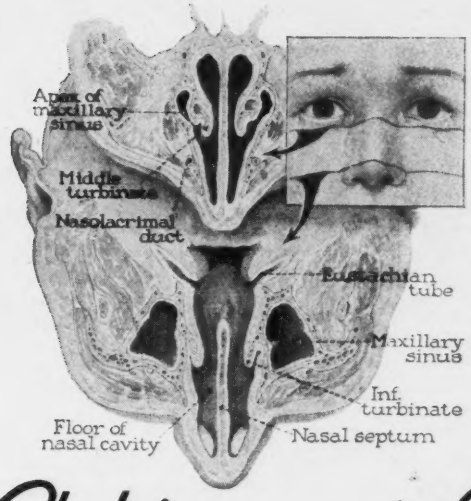


For Children and Adults

NEO-SYNEPHRIN

HYDROCHLORIDE

(levo-meta-methylaminoethanolphenol hydrochloride)

EMULSION

ACCEPTED AMERICAN MEDICAL ASSN. Council on Pharmacy and Chemistry

Reduces Nasal Engorgement in Colds

Neo-Synephrin Emulsion may be used in children as well as adults for relief of nasal congestion and discharge in colds, rhinitis and sinusitis.

The instillation of a few drops into the nasal cavities will quickly and effectively constrict the engorged mucosa without sting or other untoward effects.

SOME OF THE ADVANTAGES OF NEO-SYNEPHRIN EMULSION ARE:

1. No sting
2. More sustained action than epinephrine or ephedrine
3. Less toxic in therapeutic dosage than epinephrine or ephedrine
4. So stable that it may be sterilized by boiling
5. In the doses recommended Neo-Synephrin usually does not produce nervousness or insomnia.

DOSAGE FORMS:

NEO-SYNEPHRIN HYDROCHLORIDE EMULSION,
¼%—(1-oz. bottle with dropper)

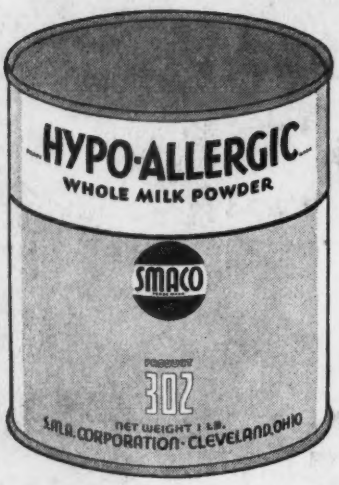
NEO-SYNEPHRIN HYDROCHLORIDE SOLUTION,
¼% for dropper or spray, 1% for resistant cases

NEO-SYNEPHRIN HYDROCHLORIDE JELLY, (1-oz. bottle)
½%—(in collapsible tubes with applicator)

FREDERICK STEARNS & COMPANY

DETROIT NEW YORK KANSAS CITY SAN FRANCISCO
WINDSOR, CANADA SYDNEY, AUSTRALIA

for Milk ALLERGY



Smaco HYPO-ALLERGIC MILK

CHARACTERISTICS of Powdered Hypo-Allergic Whole Milk (Smaco 302)

Helps prevent eczema in patients hypersensitive to milk protein.

Use present formulas since this is real cows' milk, not a substitute.

Convenience. Individual feedings may be made up for infants.

Lower cost. Powder form costs 25% less than liquid.

Spray dried in equipment reserved for Hypo-Allergic Milk and Alerdex.

It keeps. Hermetically sealed in an atmosphere of inert gas (nitrogen) to prevent deterioration.

We also offer Smaco liquid milks—Smaco (300) Hypo-Allergic WHOLE Milk and Smaco (303) Hypo-Allergic SKIM Milk.

ALERDEX, the PROTEIN-FREE maltose and dextrins

CHARACTERISTICS OF ALERDEX

Helps prevent eczemas when used routinely, due to absence of offending protein.

Use present formulas because Alerdex has same caloric value and percentage of maltose and dextrins.

Does not cake on exposure to air because it is non-hygroscopic.

Dissolves readily in warm water or milk.

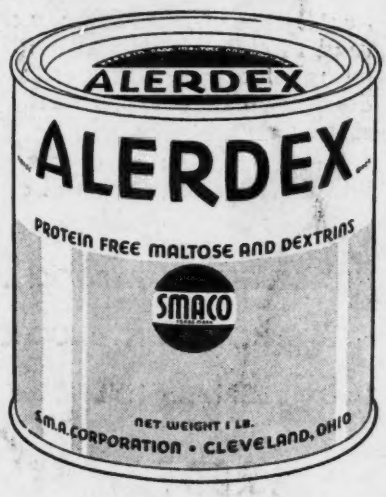
Snow white, free-flowing powder.

Inexpensive—in spite of extra processing under technical control, costs no more.

APPROXIMATE ANALYSIS OF ALERDEX

Moisture	3.0
Ash	0.5
Fat (ether extract)	0.0
Hydrolyzed protein (N x 6.25)	0.5
Reducing sugars as maltose	50.0
Dextrins (by difference)	46.0
Level tablespoons, per ounce	4
Calories, per level tablespoon	27½
Calories, per ounce	110

Alerdex is essentially a mixture of approximately equal parts of maltose and dextrins. It is prepared by a new thermally-controlled process of the enzymic hydrolysis of non-cereal starch, as a result of which it contains no protein contaminant.



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